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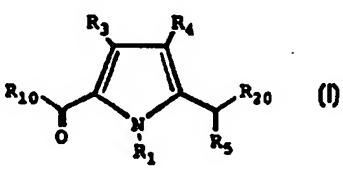
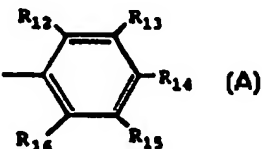
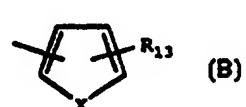
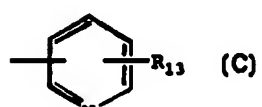
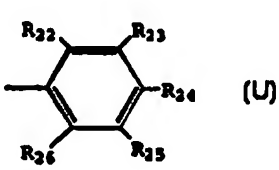
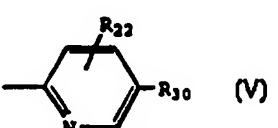
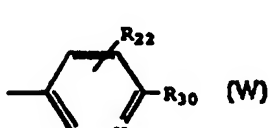
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : C07D 207/32, 207/34, 487/04, 405/12, 401/06, 409/14, 405/14, 409/06, A61K 31/40, 31/44</p>	<p>A1</p>	<p>(11) International Publication Number: <b>WO 97/46524</b>  (43) International Publication Date: 11 December 1997 (11.12.97)</p>
<p>(21) International Application Number: PCT/EP97/02587 (22) International Filing Date: 21 May 1997 (21.05.97)  (30) Priority Data: 60/018,691 30 May 1996 (30.05.96) US  (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124, Grenzacherstrasse, CH-4070 Basle (CH).  (72) Inventors: GALEAZZI TOSCANI, Edvige; Dr. Vertiz 882, Col. Narvarte, Mexico, D.F. 03020 (MX). KERTESZ, Denis, John; 459 Victory Avenue, Mountain View, CA 94043 (US). REUTER, Deborah, Carol; 1044 Webster, Palo Alto, CA 94301 (US). SJOGREN, Eric, Brian; 442 Dell Avenue, Mountain View, CA 94043 (US).  (74) Agent: GROSSNER, Lutz; 124, Grenzacherstrasse, CH-4070 Basel (CH).</p>		<p>(81) Designated States: AU, BR, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU, SG, TR, YU, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: NOVEL PYRROLE DERIVATIVES</p> <div style="text-align: center; margin: 20px 0;">  <p>(I)</p> </div> <div style="display: flex; justify-content: space-around; margin: 20px 0;"> <div style="text-align: center;">  <p>(A)</p> </div> <div style="text-align: center;">  <p>(B)</p> </div> <div style="text-align: center;">  <p>(C)</p> </div> </div> <div style="display: flex; justify-content: space-around; margin: 20px 0;"> <div style="text-align: center;">  <p>(U)</p> </div> <div style="text-align: center;">  <p>(V)</p> </div> <div style="text-align: center;">  <p>(W)</p> </div> </div> <p>(57) Abstract</p> <p>Compounds of formula (I) where R<sub>10</sub> is represented by formulae (A), (B), or (C); R<sub>20</sub> is represented by formulae (U), (V), or (W); and the other substituents are as defined in the specification; and their pharmaceutically acceptable salts; are inhibitors of prostaglandin G/H synthase and are anti-inflammatory and analgesic agents.</p>		

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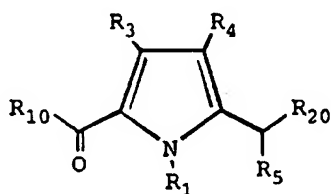


- 1 -

Novel pyrrole derivatives

This invention relates to anti-inflammatory and analgesic compounds; especially to certain 5-arylpyrrol-2-ylmethylarene derivatives, pharmaceutical compositions containing  
 5 them, methods for their use and methods for preparing these compounds.

In a first aspect, this invention provides compounds of the formula I:



10

I

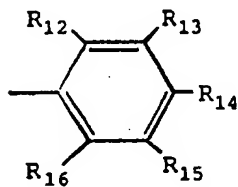
where:

$R_1$  and  $R_5$  are independently H or alkyl, or  $R_1$  and  $R_5$  together are  $-(CH_2)_2-$  or  $-(CH_2)_3-$ ;

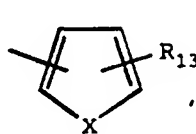
15

$R_3$  and  $R_4$  are independently H, halo, alkyl, alkyloxy, or alkylthio;

$R_{10}$  is a group represented by formula (A), (B), or (C):

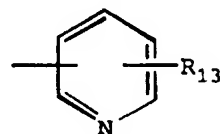


(A)



(B)

or



(C)

20 where:

X is O or S;

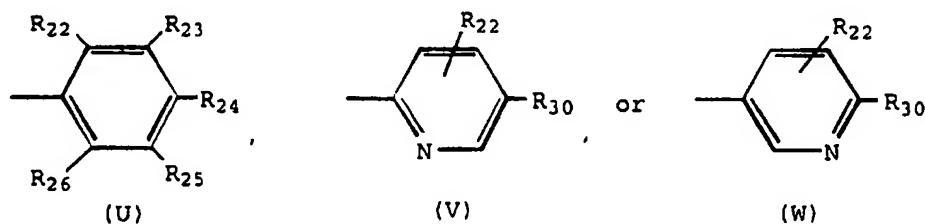
$R_{12}$  and  $R_{16}$  are independently H, halo, alkyl, alkyloxy, alkylthio, cyano, or hydroxy;

$R_{13}$  and  $R_{15}$  are independently H, halo, alkyl, alkyloxy, or alkylthio; and

25

$R_{14}$  is H, halo, alkyl, haloalkyl, amino, alkylamino, dialkylamino, alkyloxy,

- hydroxy, alkylthio, alkenyl, alkynyl, cyano,  $-\text{SO}_2\text{R}_{17}$  where  $\text{R}_{17}$  is alkyl, or  $-\text{SO}_2\text{NR}_{18}\text{R}_{19}$  where  $\text{R}_{18}$  and  $\text{R}_{19}$  are independently H or alkyl; provided that at least two of  $\text{R}_{12}$ ,  $\text{R}_{13}$ ,  $\text{R}_{14}$ ,  $\text{R}_{15}$ , and  $\text{R}_{16}$  are H, and that if only two of  $\text{R}_{12}$ ,  $\text{R}_{13}$ ,  $\text{R}_{14}$ ,  $\text{R}_{15}$ , and  $\text{R}_{16}$  are H, the non-hydrogen substituents are not all adjacent; or
- 5  $\text{R}_{12}$ ,  $\text{R}_{15}$ , and  $\text{R}_{16}$  are H and  $\text{R}_{13}$  and  $\text{R}_{14}$  together are  $-\text{OCH}_2\text{O}-$ ;  
 $\text{R}_{20}$  is a group represented by formula (U), (V), or (W):



where:

- 10  $\text{R}_{22}$  is H, halo, alkyl, cyano, trifluoromethyl, hydroxy, alkyloxy, or  $-\text{CO}_2\text{R}_{27}$  where  $\text{R}_{27}$  is H or alkyl;  
 one of  $\text{R}_{23}$ ,  $\text{R}_{24}$ , and  $\text{R}_{25}$  is  $\text{R}_{30}$ ; and  
 either all the remaining  $\text{R}_{23}$ ,  $\text{R}_{24}$ ,  $\text{R}_{25}$ , and  $\text{R}_{26}$  are H; or one of the remaining  $\text{R}_{23}$ ,  $\text{R}_{24}$ ,  $\text{R}_{25}$ , and  $\text{R}_{26}$  is halo, alkyl, cyano, trifluoromethyl, hydroxy, or alkyloxy; and
- 15  $\text{R}_{30}$  is  $-\text{OH}^*$ ,  $-\text{NHH}^*$ ,  $-\text{NH}^*\text{CHO}$ ,  $-\text{NH}^*\text{C}(\text{X})\text{R}_{31}$ ,  $-\text{NH}^*\text{SO}_2\text{R}_{31}$ ,  $-\text{NH}^*\text{C}(\text{X})\text{NR}_{32}\text{R}_{33}$ , or  $-\text{NH}^*\text{SO}_2\text{NR}_{32}\text{R}_{34}$ ;  
 where:  
 $\text{H}^*$  is hydrogen, optionally replaced by an *in vivo* hydrolyzable protecting group;  
 $\text{R}_{31}$  is alkyl, haloalkyl, hydroxyalkyl, alkenyl, benzyl, aryl, cycloamino,  
 20  $-\text{CH}_2\text{SO}_2\text{Me}$ , or  $-(\text{CH}_2)_n\text{R}_{35}$  where  $n$  is an integer from 2 to 5 and  $\text{R}_{35}$  is alkylamino, dialkylamino, cycloamino, alkyloxy, acyloxy, or  $-\text{CO}_2\text{R}_{27}$ ;  
 $\text{R}_{32}$  is H, alkyl, or  $-(\text{CH}_2)_n\text{OR}_{27}$ ;  
 $\text{R}_{33}$  is H, alkyl, haloalkyl, aryl, hydroxyalkyl, tetrahydrofuran-2-ylmethyl,  $-\text{CH}_2\text{CO}_2\text{R}_{27}$ , or  $-(\text{CH}_2)_n\text{R}_{35}$ ; and  
 25  $\text{R}_{34}$  is H, alkyl, acetyl, hydroxyalkyl, or  $-(\text{CH}_2)_n\text{R}_{35}$ ;  
 and their pharmaceutically acceptable salts.

In another aspect of invention is concerned with the use of the compounds of formula I as medicaments.

In still another aspect, this invention provides pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or its pharmaceutically acceptable salt and a pharmaceutically acceptable excipient.

5 In yet another aspect, this invention is concerned with the use of the compounds of formula I in the manufacture of pharmaceutical compositions for the treatment of an inflammatory or autoimmune disease.

Unless otherwise stated, the following terms used in the specification and claims  
10 have the meanings given below:

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms; or a branched or cyclic saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, cyclopropyl, cyclopropylmethyl,  
15 pentyl, and the like.

"Alkyloxy" means a radical -OR where R is alkyl, e.g., methoxy, ethoxy, propoxy, 2-propoxy, and the like.

20 "Alkylthio" means a radical -SR where R is alkyl, e.g., methylthio, butylthio, and the like.

"Acyloxy" means a radical -OC(O)R where R is alkyl, e.g., acetoxy, propionyloxy and the like.  
25

"Alkenyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing a double bond, e.g., ethenyl, propenyl, and the like.

30 "Alkynyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing a triple bond, e.g., ethynyl, propynyl, butynyl, and the like.

"Halo" means fluoro, bromo, chloro and iodo, preferably fluoro and chloro.  
35

"Haloalkyl" means alkyl substituted with one to three fluorine or chlorine atoms,

e.g.,  $-\text{CH}_2\text{Cl}$ ,  $-\text{CF}_3$ ,  $-\text{CH}_2\text{CF}_3$ ,  $-\text{CH}_2\text{CCl}_3$ , and the like.

"Alkylamino" means a radical  $-\text{NHR}$  where R is alkyl, e.g., methylamino, (1-methylethyl)amino, and the like.

5

"Dialkylamino" means a radical  $-\text{NRR}'$  where R and R' are independently alkyl, e.g., dimethylamino, methylethylamino, di(1-methylethyl)amino, and the like.

10 "Cycloamino" means a saturated monovalent, cyclic radical of 5 or 6 ring atoms of which the bonding ring atom is N; one non-adjacent other ring atom is NR (where R is hydrogen or alkyl), O, or C; and the remaining ring atoms are C. Examples include 1-pyrrolidino, 1-piperidino, 1-piperazino, *N*-methylpiperazino, 4-morpholino, and the like.

15 "Hydroxyalkyl" means a linear monovalent hydrocarbon radical of two to four carbon atoms or a branched monovalent hydrocarbon radical of three or four carbons substituted with one or two hydroxy groups, provided that: (1) the bonding carbon is unsubstituted, and (2) if two hydroxy groups are present, they are not both on the same carbon atom. Examples include 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 20 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

25 "Aryl" means a monovalent aromatic hydrocarbon radical of 5 or 6 ring atoms, optionally containing one ring heteroatom selected from NR (where R is H or alkyl), O or S, and optionally mono- or di-substituted independently with  $-\text{OH}$ ,  $-\text{COOH}$ , alkyl, alkyloxy, alkylthio, fluoro, chloro,  $-\text{CF}_3$ , and cyano; e.g., phenyl, thienyl, pyridyl, furanyl, 3-chlorophenyl, 4-(methylthio)phenyl, and the like.

30 An "*in vivo* hydrolyzable protecting group" means a group, replacing an acidic proton (such as a phenolic or amino proton) in a compound of formula I, that is capable of undergoing enzymatic hydrolysis within a living organism to form the unprotected (proton-containing) compound of formula I *in vivo*. Preferred *in vivo* hydrolyzable protecting groups are  $-\text{C}(\text{O})\text{R}$ , where R is alkyl, or  $-\text{C}(\text{O})\text{CH}(\text{NH}_2)\text{R}''$ , where R'' is the side chain of a 35 D or L natural amino acid [e.g., for alanine, R'' is methyl; for lysine, R'' is  $-(\text{CH}_2)_4\text{NH}_2$ ]. Preferred R'' groups are methyl, isopropyl and benzyl.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "-OH\* where H\* is optionally replaced by an *in vivo* hydrolyzable protecting group" means that the *in vivo* hydrolyzable protecting group may but need not be present, and the description includes situations where -OH\* is present as -OH, -OC(O)R, or -OC(O)CH(NH<sub>2</sub>)R" where -C(O)R and -C(O)CH(NH<sub>2</sub>)R" are *in vivo* hydrolyzable protecting groups as defined above.

10

A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

- (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or
- (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion;

or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine, and the like.

"Treating" or "treatment" of a disease includes:

5

- (1) preventing ,
- (2) inhibiting or
- (3) relieving the disease.

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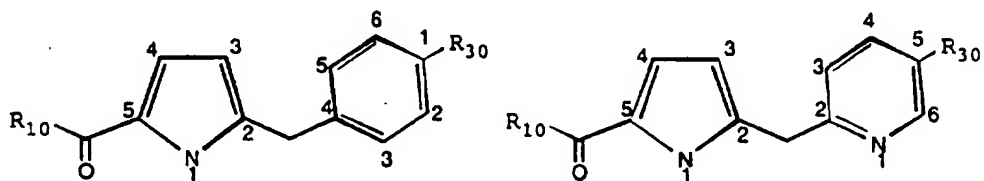
A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

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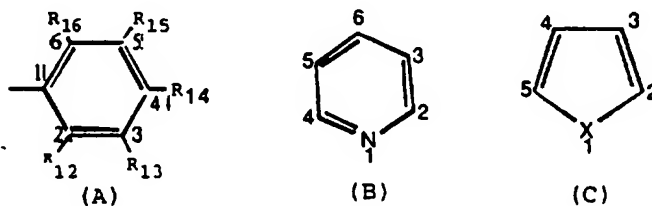
"Me" denotes methyl.

The naming and numbering of the compounds of this invention is illustrated below. The pyrrole and the side chain of  $R_{20}$  nucleus of the compounds of formula I are numbered as follows:

20



Side chains of the  $R_{10}$  substituent are numbered as shown below:



25

The pyridine, thiophene, and furan rings can be linked to the pyrrole carbonyl group at any position on the ring other than 1-position. Accordingly, the pyridine ring can

be 2-, 3-, or 4-pyridyl, the thiophene ring can be 2- or 3-thienyl, and the furan ring can be 2- or 3-furyl.

The nomenclature used in this application is generally based on the IUPAC  
 5 recommendations. However, because a strict adherence to these recommendations would result in the names changing substantially when only a single substituent is changed, compounds have been named in a form that maintains consistency of nomenclature for the basic structure of the molecule.

10 Representative compounds of this invention are as follows:

**Ia.** Compounds of formula I where  $R_1=R_3=Me$ ;  $R_4=R_{12}=R_{13}=R_{15}=R_{16}=R_{25}=H$ ,  
 $R_{14}=Cl$ ;  
 $R_{10} =$  group represented by formula (A);  $R_{20} =$  group represented by formula (U);  
 15 and  $R_{24}=R_{30}=NH*SO_2R_{31}$ , are:

CPD#	$R_5$	$R_{22}$	$R_{23}$	$R_{26}$	$R_{31}$	M. Pt. °C
1	H	H	H	H	Me	200.9-202
2	H	H	H	H	CF <sub>3</sub>	159.5-160.2
3	H	H	H	H	CH <sub>2</sub> CH <sub>3</sub>	152.1-152.9
4	H	H	H	H	(CH <sub>2</sub> ) <sub>2</sub> NMe <sub>2</sub> .HCl	232.5-232.7
5	H	H	H	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	147.6-148.2
6	H	H	H	H	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	211
7	H	H	H	H	(CH <sub>2</sub> ) <sub>2</sub> OH	132.2-134
8	H	H	H	H	(CH <sub>2</sub> ) <sub>2</sub> -morpho- line.HCl	243.4-243.7
9	H	H	H	H	CH=CH <sub>2</sub>	146.8-147
10	H	H	H	H	CH <sub>2</sub> SO <sub>2</sub> Me	187-188
11	Me	H	H	H	Me	foam
12	H	Me	H	H	Me	190-191
13	H	CF <sub>3</sub>	H	H	Me	204-206
14	H	Cl	H	H	Me	215-217
15	H	CO <sub>2</sub> Me	H	H	Me	197-199
16	H	CO <sub>2</sub> H	H	H	Me	248-250
17	H	F	H	H	Me	211-212

18	H	OMe	H	H	Me	164-165
19	H	CN	H	H	Me	204
20	H	F	H	H	CH <sub>2</sub> CH <sub>3</sub>	151-151.3
21	H	H	Me	H	Me	175-177
22	H	H	F	H	Me	183-185
23	H	H	OH	H	Me	205
24	H	H	CN	H	Me	187
25	H	Cl	H	H	(CH <sub>2</sub> ) <sub>2</sub> OH	159
26	H	H	H	H	Me     H*=COMe	196
27	H	F	H	F	Me	242.8-243.5

and are named as follows:

1. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}methane-  
5 sulfonamide.
2. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}trifluoro-  
methanesulfonamide.
- 10 3. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-  
ethanesulfonamide.
4. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-  
(dimethylamino)-ethanesulfonamide hydrochloride.
- 15 5. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-  
(methoxy-carbonyl)ethanesulfonamide.
6. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-  
20 (carboxy)-ethanesulfonamide.
7. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-  
(hydroxy)- ethanesulfonamide.



8. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(morpholin-4-yl)ethanesulfonamide hydrochloride.
9. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}ethenesulfonamide.
10. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-C-(methylsulfonyl)-methanesulfonamide.
- 10 11. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylethan-1-yl]phenyl}-methanesulfonamide, m/e = 430 (M+).
12. N-{3-Methyl-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 15 13. N-{3-Trifluoromethyl-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
14. N-{3-Chloro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 20 15. N-{3-Carboxymethyl-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 25 16. N-{3-Carboxy-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
17. N-{3-Fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 30 18. N-{3-Methoxy-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
19. N-{3-Cyano-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 35

20. N-{3-Fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-ethanesulfonamide.
21. N-{2-Methyl-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
22. N-{2-Fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
23. N-{2-Hydroxy-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
24. N-{2-Cyano-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
25. N-{3-Chloro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
26. N-Methoxycarbonyl-N-{4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
27. N-{3,5-Difluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- Ib. Compounds of formula I where  $R_1=Me$ ;  $R_4=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=H$ ;  $R_{14}=Me$ ;  $R_{10}=$  is a group represented by formula (A);  $R_{20}=$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH*SO_2R_{31}$ , are:

CPD#	$R_3$	$R_5$	$R_{12}$	$R_{22}$	$R_{26}$	$R_{31}$	M. Pt. °C
28	H	H	H	H	H	Me	138-139
29	H	H	H	H	H	$(CH_2)_2OH$	foam
30	H	Me	H	H	H	Me	147-148
31	H	H	H	Cl	H	Me	137-139
32	H	H	H	$CF_3$	H	Me	172-174

33	H	H	H	Br	H	Me	160-161
34	H	H	H	CN	H	Me	171-172
35	H	H	H	F	H	Me	164.8-165.3
36	H	H	H	F	H	(CH <sub>2</sub> ) <sub>2</sub> OH	foam
37	H	H	H	Cl	H	(CH <sub>2</sub> ) <sub>2</sub> OH	123-125
38	Me	H	H	F	H	Me	200.8-201.6
39	Me	H	H	F	H	CH <sub>2</sub> CH <sub>3</sub>	140.4-141.9
40	Me	H	H	CN	H	Me	204.3-207.4
41	H	H	Me	F	H	Me	159.6-160.0
42	H	H	H	F	H	CH(CH <sub>2</sub> OH) <sub>2</sub>	133.3-133.6
43	Me	H	Me	Cl	H	Me	191.8-192.4
44	H	H	H	F	H	(CH <sub>2</sub> ) <sub>3</sub> OH	116.7-119.8
45	Me	H	Me	CN	H	Me	203-205.2
46	Me	H	H	F	H	(CH <sub>2</sub> ) <sub>2</sub> OH	151.5-152.9
47	Me	H	H	Cl	H	Me	208.4-209.4
48	H	H	Me	F	H	(CH <sub>2</sub> ) <sub>2</sub> OH	135.4-136.8
49	Me	H	Me	F	H	Me	198.3-199
50	H	H	Me	H	H	(CH <sub>2</sub> ) <sub>2</sub> OH	63-66
51	H	H	H	F	F	(CH <sub>2</sub> ) <sub>2</sub> OH	154.2-155.2
52	H	H	H	F	F	Me	205.5-206.2
53	H	H	OMe	F	H	(CH <sub>2</sub> ) <sub>2</sub> OH	70.5-76

and are named as follows:

28. N-{4-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methane-  
sulfonamide.
29. N-{4-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-  
ethanesulfonamide, m/e = 412 (M+).
30. N-{4-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylethan-1-yl]phenyl}-  
methanesulfonamide.

31. N-{3-Chloro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
32. N-{3-Trifluoromethyl-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
33. N-{3-Bromo-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
34. N-{3-Cyano-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
35. N-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
36. N-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide, m/e = 430 (M+).
37. N-{3-Chloro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
38. N-{3-Fluoro-4-[5-(4-methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
39. N-{3-Fluoro-4-[5-(4-methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-ethanesulfonamide.
40. N-{3-Cyano-4-[5-(4-methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
41. N-{3-Fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
42. N-{3-Fluoro-4-[5-(4-methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-1-(hydroxymethyl)-2-(hydroxy)ethanesulfonamide.

43. N-{3-Chloro-4-[5-(2,4-dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-phenyl}-methanesulfonamide.
44. N-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-  
5 3-(hydroxy)propanesulfonamide.
45. N-{3-Cyano-4-[5-(2,4-dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 10 46. N-{3-Fluoro-4-[5-(4-methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
47. N-{3-Chloro-4-[5-(4-methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 15 48. N-{3-Fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
49. N-{3-Fluoro-4-[5-(2,4-dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-  
20 phenyl}-methanesulfonamide.
50. N-{4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.
- 25 51. N-{3,5-Difluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
52. N-{3,5-Difluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide
- 30 53. N-{3-Fluoro-4-[5-(2-methoxy-4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}- 2-(hydroxy)ethanesulfonamide

Ic. Compounds of formula I where  $R_1=Me$ ;  $R_4=R_5=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=H$ ;  
 $R_{14}=H$ ;

$R_{10}=$  is a group represented by formula (A);  $R_{20}=$  is a group represented by  
 formula

5 ( $U$ ); and  $R_{24}=R_{30}=NH*SO_2R_{31}$ , are:

CPD#	$R_3$	$R_{12}$	$R_{22}$	$R_{26}$	$R_{31}$	M. Pt. °C
54	Me	H	H	H	Me	149-150
55	Me	H	H	H	$(CH_2)_2CO_2Me$	121.5-121.9
56	Me	H	H	H	$(CH_2)_2CO_2H$	181
57	Me	H	H	H	$(CH_2)_2OH$	158.2-158.6
58	Me	H	H	H	$CH_2CH_3$	117.7-118.8
59	Me	H	Cl	H	Me	177-179
60	Me	H	F	H	Me	167-168
61	Me	H	OMe	H	Me	133-134
62	Me	H	$CF_3$	H	Me	170-171
63	Me	H	F	H	$(CH_2)_2OH$	149-149.3
64	H	H	H	H	Me	137-138
65	H	H	F	H	Me	137.2-137.5
66	H	H	F	H	$(CH_2)_2OH$	foam
67	Me	H	F	H	Me $H^*=COMe$	172
68	Me	H	F	H	$CH_2CH_3$	141.1-143.1
69	H	H	Cl	H	$(CH_2)_2OH$	149.9-151.1
70	H	H	Cl	H	Me	180.2-181.6
71	H	Me	F	H	Me	178.7-179.2
72	H	OMe	F	H	Me	184.4-184.9
73	H	OMe	F	H	$(CH_2)_2OH$	foam
74	H	F	F	H	Me	140-141
75	H	H	F	F	Me	192.6-193.1
76	H	Cl	F	H	$(CH_2)_2OH$	55.5-58.5
77	H	F	F	H	$(CH_2)_2OH$	54.2-58.1
78	H	H	F	F	$C_2H_5$	138.5-139.4
79	Me	H	F	F	$(CH_2)_2OH$	171-173.8
80	H	H	F	F	$(CH_2)_2OH$	156.5-157

and are named as follows:

54. N-{4-[5-Benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}methanesulfonamide.  
5
55. N-{4-[5-Benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(methoxy-carbonyl)-ethanesulfonamide.
56. N-{4-[5-Benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(carboxy)ethane-sulfonamide.  
10
57. N-{4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethane-sulfonamide.
- 15 58. N-{4-[5-Benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}ethanesulfonamide.
59. N-{3-Chloro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.
- 20 60. N-{3-Fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.
61. N-{3-Methoxy-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.  
25
62. N-{3-Trifluoromethyl-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
63. N-{3-Fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.  
30
64. N-{4-[5-Benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methanesulfonamide.
65. N-{3-Fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.  
35

66. N-{3-Fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide, m/e = 416 (M+).
- 5 67. N-Acetyl-N-{3-Fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
68. N-{3-Fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}ethanesulfonamide.
- 10 69. N-{3-Chloro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.
70. N-{3-Chloro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methanesulfonamide.
- 15 71. N-{3-Fluoro-4-[5-(2-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
72. N-{3-Fluoro-4-[5-(2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 20 73. N-{3-Fluoro-4-[5-(2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide, m/e = 446 (M+).
- 25 74. N-{3-Fluoro-4-[5-(2-fluorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
75. N-{3,5-Difluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methanesulfonamide.
- 30 76. N-{3-Fluoro-4-[5-(2-chlorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.
- 35 77. N-{3-Fluoro-4-[5-(2-fluorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.



78. N-{3,5-Difluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}ethanesulfonamide.
79. N-{3,5-Difluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.
80. N-{3,5-Difluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.
- 10 Id. Compounds of formula I where  $R_1=Me$ ;  $R_4=R_5=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{10}=$  is a group represented by formula (A);  $R_{20}=$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH^*SO_2R_{31}$ , are:

CPD#	$R_{12}$	$R_{14}$	$R_3$	$R_{22}$	$R_{31}$	M. Pt. °C
81	H	NMe <sub>2</sub>	H	H	Me	210-211
82	H	Cl	H	H	Me	164
83	H	Br	H	H	Me	169-170
84	Me	Me	H	H	Me	129-130
85	H	OMe	H	H	Me	147-148
86	H	SMe	H	H	Me	185-186
87	H	NH <sub>2</sub>	H	H	Me	203.3-205
88	H	NMe <sub>2</sub>	H	F	Me	199
89	H	NMe <sub>2</sub>	H	CN	Me	203
90	H	CH <sub>2</sub> CH <sub>3</sub>	H	H	Me	115-116
91	H	cyclo-propyl	H	H	Me	foam
92	Me	H	Me	H	Me	149-151
93	H	SMe	Me	H	Me	182.6-183.3
94	H	SMe	Me	H	CH <sub>2</sub> CH <sub>3</sub> Na <sup>+</sup>	>280
95	H	OMe	Me	F	Me	186.6-187.5
96	H	OMe	H	F	Me	180.9-181.8
97	H	OMe	Me	F	CH <sub>2</sub> CH <sub>3</sub>	109-110
98	H	OMe	Me	F	(CH <sub>2</sub> ) <sub>2</sub> OH	139.5-140.5
99	H	OMe	H	CN	Me	164.7-166.7

100	H	SMe	Me	F	CH <sub>2</sub> CH <sub>3</sub>	148.1-148.7
101	H	F	Me	F	Me	169.2-169.7
102	H	F	Me	F	CH <sub>2</sub> CH <sub>3</sub>	138.2-139.2
103	H	SMe	Me	F	Me	188.8-189.5
104	H	F	Me	F	(CH <sub>2</sub> ) <sub>2</sub> OH	139.1-140.2
105	H	OMe	Me	F	CH=CH <sub>2</sub>	90-92
106	H	OMe	H	F	(CH <sub>2</sub> ) <sub>2</sub> OH	135-137
107	H	SMe	Me	F	(CH <sub>2</sub> ) <sub>2</sub> OCOMe	146.2-146.7
108	H	SMe	Me	F	(CH <sub>2</sub> ) <sub>2</sub> OH	174.9-175.5
109	H	CF <sub>3</sub>	Me	F	Me	177-177.8
110	H	CF <sub>3</sub>	Me	F	CH <sub>2</sub> CH <sub>3</sub>	132.4-133.2
111	H	cyclo- propyl	H	F	Me	140.5-142
112	H	CF <sub>3</sub>	Me	Cl	Me	203-204.8
113	Cl	OMe	H	F	Me	150-151
114	Cl	OMe	H	F	(CH <sub>2</sub> ) <sub>2</sub> OH	
115	F	F	H	F	Me	168.4-169.1
116	F	F	H	F	(CH <sub>2</sub> ) <sub>2</sub> OH	80-84
117	H	OC <sub>2</sub> H <sub>5</sub>	H	F	Me	134.6-134.9
118	OMe	F	H	F	Me	162-162.3
119	H	OC <sub>2</sub> H <sub>5</sub>	H	F	CH <sub>2</sub> CH <sub>3</sub>	135.3-135.6
120	OMe	F	H	F	(CH <sub>2</sub> ) <sub>2</sub> OH	58.1-64.1
121	H	OC <sub>2</sub> H <sub>5</sub>	H	F	(CH <sub>2</sub> ) <sub>2</sub> OH	105-106.5
122	Me	OMe	H	F	Me	149.5-150.1
123	Me	OMe	H	F	(CH <sub>2</sub> ) <sub>2</sub> OH	56.3-61.7
124	Me	Br	H	F	Me	177.5-178
125	Me	Br	H	F	(CH <sub>2</sub> ) <sub>2</sub> OH	70.5-71.5
126	F	OMe	H	F	Me	164.5-165.1
127	H	Br	H	F	Me	178.6-179.5
128	H	Br	H	F	(CH <sub>2</sub> ) <sub>2</sub> OH	53.5-56
129	H	Cl	H	F	Me	175.4-176.1
130	H	Cl	H	F	(CH <sub>2</sub> ) <sub>2</sub> OH	143.1-144

and are named as follows:

81. N-{4-[5-(4-Dimethylaminobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methane-sulfonamide.
- 5 82. N-{4-[5-(4-Chlorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.
83. N-{4-[5-(4-Bromobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.
- 10 84. N-{4-[5-(2,4-Dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
85. N-{4-[5-(4-Methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-phenyl}-methanesulfonamide.
- 15 86. N-{4-[5-(4-Methylthiobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.
87. N-{4-[5-(4-Aminobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.
- 20 88. N-{3-Fluoro-4-[5-(4-dimethylaminobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 25 89. N-{3-Cyano-4-[5-(4-dimethylaminobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
90. N-{4-[5-(4-Ethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.
- 30 91. N-{4-[5-(4-Cyclopropylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
92. N-{4-[5-(2-Methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 35

93. N-{4-[5-(4-Methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methane-sulfonamide.
94. N-{4-[5-(4-Methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}ethane-sulfonamide sodium salt.
95. N-{3-Fluoro-4-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
96. N-{3-Fluoro-4-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
97. N-{3-Fluoro-4-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-ethanesulfonamide.
98. N-{3-Fluoro-4-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
99. N-{3-Cyano-4-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
100. N-{3-Fluoro-4-[5-(4-methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-ethanesulfonamide.
101. N-{3-Fluoro-4-[5-(4-fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
102. N-{3-Fluoro-4-[5-(4-fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-ethanesulfonamide.
103. N-{3-Fluoro-4-[5-(4-methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
104. N-{3-Fluoro-4-[5-(4-fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.

105. N-{3-Fluoro-4-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-ethanesulfonamide.
106. N-{3-Fluoro-4-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-  
5 2-(hydroxy)ethanesulfonamide.
107. N-{3-Fluoro-4-[5-(4-methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(acetoxy)ethanesulfonamide.
- 10 108. N-{3-Fluoro-4-[5-(4-methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
109. N-{3-Fluoro-4-[5-(4-trifluoromethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 15 110. N-{3-Fluoro-4-[5-(4-trifluoromethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-ethanesulfonamide.
111. N-{3-Fluoro-4-[5-(4-cyclopropylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 20 112. N-{3-Chloro-4-[5-(4-trifluoromethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- 25 113. N-{3-Fluoro-4-[5-(2-chloro-4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
114. N-{3-Fluoro-4-[5-(2-chloro-4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide, m/e = 481 (M+H).
- 30 115. N-{3-Fluoro-4-[5-(2,4-difluorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
116. N-{3-Fluoro-4-[5-(2,4-difluorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-  
35 2-(hydroxy)ethanesulfonamide.

117. N-{3-Fluoro-4-[5-(4-ethoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
118. N-{3-Fluoro-4-[5-(4-fluoro-2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
119. N-{3-Fluoro-4-[5-(4-ethoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-ethanesulfonamide.
120. N-{3-Fluoro-4-[5-(4-fluoro-2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
121. N-{3-Fluoro-4-[5-(4-ethoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
122. N-{3-Fluoro-4-[5-(4-methoxy-2-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
123. N-{3-Fluoro-4-[5-(4-methoxy-2-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
124. N-{3-Fluoro-4-[5-(4-bromo-2-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
125. N-{3-Fluoro-4-[5-(4-bromo-2-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
126. N-{3-Fluoro-4-[5-(2-fluoro-4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
127. N-{3-Fluoro-4-[5-(4-bromobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
128. N-{3-Fluoro-4-[5-(4-bromobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.

129. N-{3-Fluoro-4-[5-(4-chlorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.

5 130. N-{3-Fluoro-4-[5-(4-chlorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.

10 Ie. Compounds of formula I where  $R_1+R_5=-(CH_2)_2-$ ;  $R_3=R_4=R_{12}=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH*SO_2R_{31}$ , are:

CPD#	$R_{14}$	$R_{22}$	$R_{31}$	M. Pt. °C
131	H	Cl	Me	85-95
132	OMe	Cl	Me	183-183.5
133	OMe	Cl	$(CH_2)_2OH$	74.5-84.5
134	H	Cl	$(CH_2)_2OH$	80.5-109
135	H	F	Me	162-162.8
136	OMe	H	Me	146-147.1
137	OMe	F	$(CH_2)_2OH$	146-147.1
138	OMe	F	Me	159-162
139	H	F	$(CH_2)_2OH$	159-161.5

and are named as follows:

15 131. N-{3-Chloro-4-[5-Benzoyl-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}methanesulfonamide.

132. N-{3-Chloro-4-[5-(4-methoxybenzoyl)-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}-methanesulfonamide.

20

133. N-{3-Chloro-4-[5-(4-methoxybenzoyl)-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}-2-(hydroxy)ethanesulfonamide.

25

134. N-{3-Chloro-4-[5-benzoyl-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}-2-(hydroxy)-ethanesulfonamide.

135. N-{3-Fluoro-4-[5-benzoyl-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}methane-sulfonamide.
- 5 136. N-{4-[5-(4-methoxybenzoyl)-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}methane-sulfonamide.
137. N-{3-Fluoro-4-[5-(4-methoxybenzoyl)-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}-2-(hydroxy)-ethanesulfonamide.
- 10 138. N-{3-Fluoro-4-[5-(4-methoxybenzoyl)-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}-methanesulfonamide.
139. N-{3-Fluoro-4-[5-benzoyl-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}-2-(hydroxy)-ethanesulfonamide.
- 15 IIa. Compounds of formula I where  $R_1=R_3=Me$ ;  $R_4=R_5=R_{12}=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{14}=Cl$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH*SO_2NR_{32}R_{34}$ , are:

20

CPD#	$R_{22}$	$R_{32}$	$R_{34}$	M. Pt. °C
140	H	Me	Me	57-142
141	H	H	H	175-177
132	H	H	COCH <sub>3</sub>	164.5-170
143	H	(CH <sub>2</sub> ) <sub>2</sub> OH	(CH <sub>2</sub> ) <sub>2</sub> OH	122-124
144	Cl	Me	Me	175-177
145	F	Me	Me	185-186
146	F	H	H	179.8-180
147	CN	H	H	192
148	Cl	H	H	179-180

and are named as follows:

140. 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
- 25



141. 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}sulfamide.
142. 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-  
5 acetylsulfamide.
143. 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-phenyl}-3,3-bis-(2-hydroxyethyl)sulfamide.
- 10 144. 1-{3-Chloro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
145. 1-{3-Fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-di-methylsulfamide.
- 15 146. 1-{3-Fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
147. 1-{3-Cyano-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-  
20 sulfamide.
148. 1-{3-Chloro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
- 25 IIb. Compounds of formula I where  $R_1=Me$ ;  $R_4=R_5=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=H$ ;  $R_{14}=Me$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH*SO_2NR_{32}R_{34}$ , are:

CPD#	$R_3$	$R_{12}$	$R_{22}$	$R_{26}$	$R_{32}$	$R_{34}$	M. P. °C
149	H	H	H	H	Me	Me	130-139
150	H	H	H	H	H	H	152-152.8
151	H	H	Cl	H	Me	Me	157-159
152	H	H	CF <sub>3</sub>	H	Me	Me	114-115
153	H	H	Br	H	Me	Me	157-158
154	H	H	F	H	H	H	153.1-153.9

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155	H	H	F	H	Me	Me	158-158.9
156	H	H	Cl	H	H	H	166.3-166.9
157	H	H	F	H	(CH <sub>2</sub> ) <sub>2</sub> OH	(CH <sub>2</sub> ) <sub>2</sub> OH	108.4-108.7
158	H	H	F	H	H	Me	foam
159	H	H	F	H	H	CH <sub>2</sub> CH <sub>3</sub>	foam
160	H	H	F	H	H	(CH <sub>2</sub> ) <sub>2</sub> OMe	foam
161	Me	H	F	H	H	Me	166.5-167.
162	Me	H	F	H	H	H	189.5-189.9
163	Me	H	F	H	Me	Me	169.6-170.5
164	H	H	F	H	H	(CH <sub>2</sub> ) <sub>2</sub> OH	120.2-121.8
165	H	Me	F	H	H	H	149-152
166	Me	Me	Cl	H	Me	Me	58.9-61.8
167	Me	Me	Cl	H	H	H	76.5-80.2
168	H	Me	H	H	H	CH <sub>2</sub> CH <sub>3</sub>	66-70
169	H	Me	H	H	H	H	77-88.6
170	H	Me	H	H	H	Me	76-80
171	Me	Me	CN	H	H	H	161.5-165
172	H	Me	F	H	H	Me	65.1-67.5
173	Me	Me	CN	H	Me	Me	67-71
174	H	H	F	F	H	H	202.2-202.8
175	H	Me	F	H	H	COCH <sub>3</sub>	94-97.5

and are named as follows:

149. 1-{4-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-  
5 dimethylsulfamide.
150. 1-{4-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}sulfamide.
151. 1-{3-Chloro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-  
10 di-methylsulfamide.
152. 1-{3-Trifluoromethyl-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.

153. 1-{3-Bromo-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-di-methylsulfamide.
- 5 154. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
155. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-di-methylsulfamide.
- 10 156. 1-{3-Chloro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
157. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-bis-(2-hydroxyethyl)sulfamide.
- 15 158. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-methyl-sulfamide, m/e = 415 (M+).
- 20 159. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-ethyl-sulfamide, m/e = 429 (M+).
160. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-(2-methoxyethyl)sulfamide, m/e = 459 (M+).
- 25 161. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-methyl-sulfamide.
162. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
- 30 163. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-di-methylsulfamide.
164. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-(2-hydroxyethyl)sulfamide.
- 35

165. 1-{3-Fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
166. 1-{3-Chloro-4-[5-(2,4-dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-phenyl}-3,3-dimethylsulfamide.
167. 1-{3-Chloro-[5-(2,4-dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-phenyl}sulfamide.
168. 1-{4-[5-(2,4-Dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-ethylsulfamide.
169. 1-{4-[5-(2,4-Dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}sulfamide.
170. 1-{4-[5-(2,4-Dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-methylsulfamide.
171. 1-{3-Cyano-4-[5-(2,4-dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-phenyl}-sulfamide.
172. 1-{3-Fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-methylsulfamide.
173. 1-{3-Cyano-4-[5-(2,4-dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-phenyl}-3,3-dimethylsulfamide.
174. 1-{3,5-Difluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-phenyl}sulfamide.
175. 1-{3-Fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-acetyl-sulfamide.

IIc. Compounds of formula I where  $R_1=Me$ ;  $R_4=R_5=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=H$ ,  $R_{14}=H$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH*SO_2NR_{32}R_{34}$ , are:

CPD#	$R_3$	$R_{12}$	$R_{22}$	$R_{26}$	$R_{32}$	$R_{34}$	M. Pt. °C
176	Me	H	H	H	Me	Me	126.5-127.4
177	Me	H	H	H	H	H	179.1-180
178	Me	H	Cl	H	Me	Me	185-187
179	Me	H	F	H	Me	Me	182-183
180	Me	H	OMe	H	Me	Me	166-167
181	Me	H	CF <sub>3</sub>	H	Me	Me	164-165
182	H	H	F	H	H	H	168.6-169.2
183	H	H	CN	H	H	H	176.4-176.8
184	H	H	Cl	H	H	H	167.4-168.3
185	H	Cl	F	H	Me	H	99-150.5
186	H	Cl	F	H	Me	Me	68.4-69.8
187	H	Cl	F	H	H	H	171.8-172.6
188	H	F	F	H	Me	Me	114.4-114.9
189	H	H	F	F	H	H	199.8-200.2
190	H	H	F	F	H	Me	179-180.5
191	H	OMe	F	H	H	H	144.7-146
192	H	Me	F	H	H	H	186.3-186.6
193	Me	H	F	F	H	H	222.5-223
194	H	H	F	F	Me	Me	158-159.3

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and are named as follows:

176. 1-{4-[5-Benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.

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177. 1-{4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}sulfamide.

178. 1-{3-Chloro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.

15

179. 1-{3-Fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
180. 1-{3-Methoxy-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
181. 1-{3-Trifluoromethyl-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
182. 1-{3-Fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}sulfamide.
183. 1-{3-Cyano-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}sulfamide.
184. 1-{3-Chloro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}sulfamide.
185. 1-{3-Fluoro-4-[5-(2-chlorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-methylsulfamide.
186. 1-{3-Fluoro-4-[5-(2-chlorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
187. 1-{3-Fluoro-4-[5-(2-chlorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
188. 1-{3-Fluoro-4-[5-(2-fluorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
189. 1-{3,5-Difluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}sulfamide.
190. 1-{3,5-Difluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-methylsulfamide.
191. 1-{3-Fluoro-4-[5-(2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.

192. 1-{3-Fluoro-4-[5-(2-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
193. 1-{3,5-Difluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
194. 1-{3,5-Difluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
- 10 IIId. Compounds of formula I where  $R_1=Me$ ;  $R_4=R_5=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{10}=$  is a group represented by formula (A);  $R_{20}=$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH*SO_2NR_{32}R_{34}$ , are:

CPD#	$R_{12}$	$R_{14}$	$R_3$	$R_{22}$	$R_{32}$	$R_{34}$	M. Pt. °C
195	H	OMe	H	H	Me	Me	147-148
196	H	OMe	H	F	H	H	133
197	H	OMe	Me	F	H	H	175-176.5
198	H	OMe	Me	F	Me	Me	165.3-166.2
199	H	SMe	H	H	Me	Me	117-118
200	H	SMe	Me	H	Me	Me	161.4-163.2
201	H	NMe <sub>2</sub>	H	F	H	H	193
202	H	OMe	H	CN	H	H	193
203	H	NMe <sub>2</sub>	H	CN	H	H	185
204	H	F	Me	F	H	H	184.8-185.2
205	H	F	Me	F	Me	Me	151-151.4
206	H	F	Me	F	H	Me	128-129
207	H	SMe	Me	F	Me	Me	177.8-178.3
208	H	CF <sub>3</sub>	Me	F	Me	Me	188-189
209	H	cyclo-propyl	H	F	Me	Me	128.6-129.2
210	H	CF <sub>3</sub>	Me	F	H	Me	179-179.9
211	H	CF <sub>3</sub>	Me	Cl	H	H	200-201
212	F	F	H	F	H	Me	90-92
213	H	OC <sub>2</sub> H <sub>5</sub>	H	F	Me	Me	158.2-158.7

214	OMe	F	H	F	Me	Me	159-160
215	OMe	F	H	F	H	Me	152.2-157.5
216	H	OC <sub>2</sub> H <sub>5</sub>	H	F	H	H	152.4-153.2
217	Me	OMe	H	F	H	H	157.7-158.3
218	Me	Br	H	F	H	H	162.3-162.9
219	OMe	F	H	F	H	H	101.4-108.5
220	F	OMe	H	F	H	H	168.9-171.5
221	H	Cl	H	F	H	H	190-190.3

and are named as follows:

- 5 195. 1-{4-[5-(4-Methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
196. 1-{3-Fluoro-4-[5-(4-Methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
- 10 197. 1-{3-Fluoro-4-[5-(4-Methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
198. 1-{3-Fluoro-4-[5-(4-Methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-di-methylsulfamide.
- 15 199. 1-{4-[5-(4-Methylthiobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethyl-sulfamide.
200. 1-{4-[5-(4-Methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
- 20 201. 1-{3-Fluoro-4-[5-(4-dimethylaminobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
- 25 202. 1-{3-Cyano-4-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.



203. 1-{3-Cyano-4-[5-(4-dimethylaminobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-phenyl}-sulfamide.
204. 1-{3-Fluoro-4-[5-(4-fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-  
5 sulfamide.
205. 1-{3-Fluoro-4-[5-(4-fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-  
3,3-di-methylsulfamide.
- 10 206. 1-{3-Fluoro-4-[5-(4-fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-  
3-methylsulfamide.
207. 1-{3-Fluoro-4-[5-(4-methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-  
phenyl}-3,3-di-methylsulfamide.
- 15 208. 1-{3-Fluoro-4-[5-(4-trifluoromethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-  
ylmethyl]phenyl}-3,3-dimethylsulfamide.
209. 1-{3-Fluoro-4-[5-(4-cyclopropylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-  
20 3,3-di-methylsulfamide.
210. 1-{3-Fluoro-4-[5-(4-trifluoromethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-  
ylmethyl]phenyl}-3-methylsulfamide.
- 25 211. 1-{3-Chloro-4-[5-(4-trifluoromethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-  
ylmethyl]phenyl}-sulfamide.
212. 1-{3-Fluoro-4-[5-(2,4-difluorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-  
3-methylsulfamide.
- 30 213. 1-{3-Fluoro-4-[5-(4-ethoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-  
3,3-dimethylsulfamide.
214. 1-{3-Fluoro-4-[5-(4-fluoro-2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-  
35 ylmethyl]phenyl}-3,3-dimethylsulfamide.

215. 1-{3-Fluoro-4-[5-(4-fluoro-2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-methylsulfamide.
216. 1-{3-Fluoro-4-[5-(4-ethoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
217. 1-{3-Fluoro-4-[5-(4-methoxy-2-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
218. 1-{3-Fluoro-4-[5-(4-bromo-2-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
219. 1-{3-Fluoro-4-[5-(4-fluoro-2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
220. 1-{3-Fluoro-4-[5-(2-fluoro-4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
221. 1-{3-Fluoro-4-[5-(4-chlorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}sulfamide.
- IIe.** Compounds of formula (I) where  $R_1+R_5=-(CH_2)_2-$ ;  $R_3=R_4=R_{12}=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{10}=$  is a group represented by formula (A);  $R_{20}=$  is a group represented by formula (U); and  $R_{24}=R_{30}=NHSO_2NR_{32}R_{34}$ , are:

CPD#	$R_{14}$	$R_{22}$	$R_{32}$	$R_{34}$	M. Pt. °C
222	H	Cl	H	H	115-126
223	OMe	Cl	H	H	112-130
224	H	F	H	H	
225	OMe	F	H	H	117.5-172.9

and are named as follows:

222. 1-{3-Chloro-4-[5-benzoyl-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}sulfamide.

223. 1-{3-Chloro-4-[5-(4-methoxybenzoyl)-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}sulfamide.
224. 1-{3-Fluoro-4-[5-benzoyl-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}sulfamide.
- 5 225. 1-{3-Fluoro-4-[5-(4-methoxybenzoyl)-1,2-dihydro-3H-pyrrolizin-1-yl]phenyl}sulfamide.

- 10 **IIIa.** Compounds of formula I where  $R_1=R_3=Me$ ;  $R_4=R_5=R_{12}=R_{13}=R_{15}=R_{16}=R_{22}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{14}=Cl$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH^*C(O)NR_{32}R_{33}$ , are:

CPD#	$R_{32}$	$R_{33}$	M. Pt. °C
226	Me	Me	199-201.9
227	H	phenyl	213.5-214.5
228	H	3-Cl-phenyl	219.5-221.5
229	H	$CH_2CO_2H$	193.3-194
230	H	$(CH_2)_2OH$	209.6-210.2
231	H	H	214.6-215

and are named as follows:

- 15 226. 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylurea.
- 20 227. 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-phenylurea.
228. 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-(3-chlorophenyl)-urea.
- 25 229. 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-carboxy-methylurea.

230. 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-(2-hydroxy-ethyl)-urea.

231. 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}urea.

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IIIb. Compounds of formula I where  $R_1=Me$ ;  $R_3=R_4=R_5=R_{12}=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{14}=Me$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH^*C(O)NR_{32}R_{33}$ , are:

CPD#	$R_{22}$	$R_{32}$	$R_{33}$	M. Pt. °C
232	H	Me	Me	167.2-167.7
233	H	H	H	188.4-189.9
234	F	H	$(CH_2)_2OH$	193.7-194.7

10

and are named as follows:

232. 1-{4-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylurea.

15

233. 1-{4-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}urea.

234. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-3-(2-hydroxyethyl)urea.

20

IV. Compounds of formula I where  $R_1=R_3=Me$ ;  $R_4=R_5=R_{12}=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH^*C(S)NR_{32}R_{33}$ , are:

CPD#	$R_{14}$	$R_{22}$	$R_{32}$	$R_{33}$	M. Pt. °C
235	Cl	H	H	$CH_2CH_3$	80-82
236	Cl	H	H	Me	80-82
237	Cl	H	H	phenyl	158.3-159
238	Cl	H	H	2-Cl-phenyl	164.5-166
239	Cl	H	H	4-Cl-phenyl	176-177.5
240	Me	F	H	tetrahydro-furan-2-yl-methyl	131.4-132

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and are named as follows:

235. 1-{4-[5-(4-Chlorobenzoyl)-1,2-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-ethyl-2-thiourea.
- 10 236. 1-{4-[5-(4-Chlorobenzoyl)-1,2-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-methyl-2-thiourea.
- 15 237. 1-{4-[5-(4-Chlorobenzoyl)-1,2-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-phenyl-2-thiourea.
238. 1-{4-[5-(4-Chlorobenzoyl)-1,2-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-(2-chlorophenyl)-2-thiourea.
- 20 239. 1-{4-[5-(4-Chlorobenzoyl)-1,2-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-(4-chlorophenyl)-2-thiourea.
240. 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1,2-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-(tetra-hydrofuran-2-ylmethyl)-2-thiourea.

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- V. Compounds of formula I where  $R_1=R_3=Me$ ;  $R_4=R_5=R_{12}=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{14}=Cl$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH^*C(O)R_{31}$ , are:

CPD#	$R_{22}$	$R_{31}$	M. Pt. °C
241	H	Me	189-189.9
242	H	$CF_3$	231.5-234.5
243	H	$CH_2F$	180.5-181.7
244	F	Me	184.3-185.1
245	H	morpholino	209.5-210.5
246	H	4-Me piperazino	141.8-142.6
247	H	piperazino	>280
248	H	piperazino.HCl	>280
249	H	pyrrolidino	217.5-218.4

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and are named as follows:

241. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}acetamide.
- 10 242. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-trifluoroacetamide.
243. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-fluoroacetamide.
- 15 244. N-{3-Fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-acetamide.
- 20 245. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}morpholin-4-ylcarboxamide.
246. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-(4-methyl-piperazin-1-yl)carboxamide.

247. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}piperazin-1-yl-carboxamide.
248. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}piperazin-1-yl-carboxamide hydrochloride.
249. N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}pyrrolidin-1-yl-carboxamide.
- 10 VI. Compounds of formula I where  $R_1=Me$ ;  $R_4=R_5=R_{13}=R_{15}=R_{16}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{10}=$  is a group represented by formula (A);  $R_{20}=$  is a group represented by formula (U); and  $R_{24}=R_{30}=NHH^*$  are:

CPD#	$R_3$	$R_{12}$	$R_{14}$	$R_{22}$	$R_{30}$	M. Pt. °C
250	Me	H	Cl	H	NH <sub>2</sub>	142.8-145.5
251	Me	H	SMe	F	NH <sub>2</sub>	199.1-199.7
252	H	H	OMe	F	NH <sub>2</sub>	146.4-147.7
253	H	H	Me	F	NH <sub>2</sub>	142.4-143
254	H	H	H	F	NH <sub>2</sub>	130.3-131.2
255	Me	Me	Me	CN	NH <sub>2</sub>	179.8-181.9
256	Me	Me	Me	Cl	NH <sub>2</sub>	120-121.5
257	Me	H	H	F	NHC(O)CH(NH <sub>2</sub> ) - CH(Me) <sub>2</sub> (S)	130.6-131.5
258	Me	H	Me	Cl	NH <sub>2</sub>	
259	Me	H	CF <sub>3</sub>	Cl	NH <sub>2</sub>	140-140.8
260	H	Cl	H	F	NH <sub>2</sub>	97.9-99
261	H	OMe	H	F	NH <sub>2</sub>	131.4-132.6
262	Me	Me	Me	Cl	NH H*=COCH <sub>3</sub>	153-155

15 and are named as follows:

250. 4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline.
251. 3-Fluoro-4-[5-(4-methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline.

252. 3-Fluoro-4-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline.
253. 3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline.
- 5 254. 3-Fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]aniline.
255. 3-Cyano-4-[5-(2,4-dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline.
256. 3-Chloro-4-[5-(2,4-dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline.
- 10 257. N-(S)-Valyl-3-fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]aniline.
258. 3-Chloro-4-[5-(4-methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline, m/e = 352 (M+H).
- 15 259. 3-Chloro-4-[5-(4-trifluoromethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline.
260. 3-Fluoro-4-[5-(2-chlorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline.
- 20 261. 3-Fluoro-4-[5-(2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline.
262. N-{3-Chloro-4-[5-(2,4-dimethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-acetamide.
- 25 VIIa. Compounds of formula I where  $R_1=R_3=Me$ ;  $R_4=R_5=R_{12}=R_{15}=R_{16}=H$ ;  $R_{14}=Cl$ ;  $R_{10}=$  is a group represented by formula (A);  $R_{20}=$  is a group represented by formula (V); and  $R_{30}=NH*SO_2R_{31}$ , are:

CPD#	$R_{13}$	$R_{22}$	$R_{31}$	M. Pt. °C
263	H	H	Me	191
264	H	H	Me Na <sup>+</sup>	>280
265	H	H	Me HCl	199-200
266	H	H	CH <sub>2</sub> CH <sub>3</sub>	181-182
267	H	H	(CH <sub>2</sub> ) <sub>2</sub> OH	160-161



268	Cl	H	Me	161.7-162.3
269	Cl	H	CH <sub>2</sub> CH <sub>3</sub>	67.8-78.8
270	Cl	H	2-thienyl	111-114

and are named as follows:

- 5      263. N-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.
264. N-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide sodium salt.
- 10    265. N-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide hydrochloride.
266. N-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-ethanesulfonamide.
- 15    267. N-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-2-(hydroxy)ethanesulfonamide.
268. N-{2-[5-(3,4-Dichlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.
- 20    269. N-{2-[5-(3,4-Dichlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-ethanesulfonamide.
- 25    270. N-{2-[5-(3,4-Dichlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-thiophen-2-ylsulfonamide.

**VIIb.** Compounds of formula I where  $R_1=Me$ ;  $R_5=R_{13}=R_{15}=R_{16}=H$ ;  $R_{14}=Me$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (V); and  $R_{30}=NH*SO_2R_{31}$ , are:

CPD#	$R_3$	$R_4$	$R_{12}$	$R_{22}$	$R_{31}$	M. Pt. °C
271	H	H	H	H	Me	158.7-159.5
272	H	H	H	H	$(CH_2)_2OH \cdot HCl$	129
273	Me	H	H	H	Me	179-180
274	Me	H	H	H	$CH_2CH_3$	56
275	Me	H	H	H	$CH(CH_3)_2$	73
276	H	H	H	3-Cl	Me	188.2-190
277	H	H	Me	H	Me $\cdot HCl$	81-83.5
278	H	Cl	H	H	Me	142.5-142.9

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and are named as follows:

271. N-{2-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}methane-sulfonamide.
- 10 272. N-{2-[5-(4-Methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-2-(hydroxy)-ethanesulfonamide hydrochloride.
- 15 273. N-{2-[5-(4-Methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}methane-sulfonamide.
- 20 274. N-{2-[5-(4-Methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}ethane-sulfonamide.
275. N-{2-[5-(4-Methylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-(2-propane)sulfonamide.
276. N-{3-Chloro-2-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.

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277. N-{2-[5-(2,4-Dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide hydrochloride salt.

278. N-{2-[5-(4-Methylbenzoyl)-1-methyl-4-chloro-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.

VIIIc. Compounds of formula I where  $R_1 = \text{Me}$ ;  $R_4 = R_5 = R_{12} = R_{13} = R_{15} = R_{16} = \text{H}$ ;  $R_{10} =$  is a group represented by formula (A);  $R_{20} =$  is a group represented by formula (V); and  $R_{30} = \text{NH} \cdot \text{SO}_2 R_{31}$ , are:

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CPD#	$R_3$		$R_{14}$	$R_{22}$	$R_{31}$
	M. Pt. °C				
279	Me	H	H	Me .HCl	204-206
280	Me	H	H	$\text{CH}_2\text{CH}_3$	117-118
281	Me	H	H	$(\text{CH}_2)_2\text{OH} \cdot \text{HCl}$	151.5-153
282	Me	SMe	H	$\text{CH}_2\text{CH}_3$	210-215
283	Me	SMe	H	Me	175
284	Me	OMe	3-Cl	Me	178-180
285	Me	OMe	H	$\text{CH}_2\text{CH}_3$	53.8-64.7
286	Me	F	H	$\text{CH}_2\text{CH}_3$	145.5-146.2
287	Me	F	H	Me	166.1-167.2
288	H	OMe	H	Me	141-142
289	Me	OMe	H	Me	149.4-150.2

and are named as:

279. N-{2-[5-Benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}methanesulfonamide hydrochloride.

280. N-{2-[5-Benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}ethanesulfonamide.

281. N-{2-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-2-(hydroxy)ethanesulfonamide.

282. N-{2-[5-(4-Methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-ethanesulfonamide.
283. N-{2-[5-(4-Methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.
284. N-{3-Chloro-2-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.
285. N-{2-[5-(4-Methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}ethane-sulfonamide.
286. N-{2-[5-(4-Fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}ethane-sulfonamide.
287. N-{2-[5-(4-Fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.
288. N-{2-[5-(4-Methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.
289. N-{2-[5-(4-Methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide
- VIII. Compounds of formula I where  $R_1=Me$ ;  $R_4=R_5=R_{13}=R_{15}=R_{16}=H$ ;  $R_{10}=$  is a group represented by formula (A);  $R_{20}=$  is a group represented by formula (V); and  $R_{30}=NH*SO_2NR_{32}R_{34}$ , are:

CPD#	$R_{12}$	$R_{14}$	$R_3$	$R_{22}$	$R_{32}$	$R_{34}$	M. Pt. °C
290	H	Cl	Me	H	Me	Me	154-155.9
291	H	Cl	Me	H	H	H	170-171
292	H	Me	H	H	Me	Me	135-136.5
293	H	Me	H	H	H	H	168.8-169.1
294	H	H	Me	H	Me	Me	146-146.6
295	H	H	Me	H	H	H	162-163

296	H	SMe	Me	H	Me	Me	154.9-159.5
297	H	OMe	Me	3-Cl	H	H	179.8-180.2
298	H	Cl	Me	H	H	Me	175.5-176.1
299	H	Cl	Me	H	H	CH <sub>2</sub> CH <sub>3</sub>	167.3-168.1
300	H	Me	H	H	H	CH <sub>2</sub> CH <sub>3</sub>	162-163.7
301	H	SMe	Me	H	H	H	175.3-175.7
302	H	F	Me	H	Me	Me	117.3-117.8
303	H	Me	H	H	H	Me	60.3-61.3
304	H	F	Me	H	H	Me	137-142.2
305	H	F	Me	H	H	CH <sub>2</sub> CH <sub>3</sub>	163-163.5
306	H	OMe	H	H	H	H	179.8-180.2
307	Me	Me	H	H	H	Me	124-130

and are named as follows:

290. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3,3-di-methylsulfamide.
291. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}sulfamide.
292. 1-{2-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3,3-dimethyl-sulfamide.
293. 1-{2-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}sulfamide.
294. 1-{2-[5-Benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3,3-dimethylsulfamide.
295. 1-{2-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}sulfamide.
296. 1-{2-[5-(4-Methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3,3-di-methylsulfamide.

297. 1-{3-Chloro-2-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3,3-dimethylsulfamide.
298. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-methyl-sulfamide.
299. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-ethyl-sulfamide.
300. 1-{2-[5-(4-Chlorobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-ethylsulfamide.
301. 1-{2-[5-(4-Methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}sulfamide.
302. 1-{2-[5-(4-Fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3,3-di-methylsulfamide.
303. 1-{2-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-methylsulfamide.
304. 1-{2-[5-(4-Fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-methyl-sulfamide.
305. 1-{2-[5-(4-Fluorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-ethyl-sulfamide.
306. 1-{2-[5-(4-Methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}sulfamide.
307. 1-{2-[5-(2,4-Dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-methyl-sulfamide.

- IX. Compounds of formula I where  $R_1=R_3=Me$ ;  $R_4=R_5=R_{12}=R_{13}=R_{15}=R_{16}=R_{22}=H$ ;  $R_{14}=Cl$ ;  $R_{10}=$  is a group represented by formula (A);  $R_{20}=$  is a group represented by formula (V); and  $R_{30}=NH^*C(O)NR_{32}R_{33}$ , are:

CPD#	$R_{32}$	$R_{33}$	M. Pt. °C
308	Me	Me	227-230
309	H	Me	234-235.5
310	H	$(CH_2)_2Cl$	181.8-182.9
311	H	phenyl	194.5-195.2
312	H	3-Cl-phenyl	167.5-168.2
313	H	2-Cl-phenyl	186-188

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and are named as follows:

308. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3,3-di-methylurea.
- 10 309. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-methylurea.
- 15 310. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-(2-chloro-ethyl)urea.
311. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-phenylurea.
- 20 312. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-(3-chlorophenyl)urea.
313. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-(2-chlorophenyl)urea.

25

- X. Compounds of formula I where  $R_1 = \text{Me}$ ;  $R_4 = R_5 = R_{12} = R_{13} = R_{15} = R_{16} = R_{22} = \text{H}$ ;  $R_{10} =$  is a group represented by formula (A);  $R_{20} =$  is a group represented by formula (V); and  $R_{30} = \text{NH}^* \text{C}(\text{S}) \text{NR}_{32} \text{R}_{33}$ , are:

CPD#	$R_3$	$R_{14}$	$R_{22}$	$R_{32}$	$R_{33}$	M. Pt. °C
314	Me	Cl	H	H	$\text{CH}_2\text{CH}_3$	139-142
315	Me	Cl	H	H	Me	135
316	Me	Cl	H	H	phenyl	154.2-155.5
317	Me	Cl	H	H	cyclohexyl	146-150
318	Me	Cl	H	H	$(\text{CH}_2)_2\text{OMe}$	136.1-137.9
319	Me	Cl	H	H	tetrahydro-furan-2-ylmethyl	130.6-133.1
320	Me	Cl	H	H	$\text{CH}_2\text{CO}_2\text{Me}$	155-156.5
321	Me	Cl	H	H	cyclopropyl	110-122.5
322	Me	Cl	H	H	$(\text{CH}_2)_2$ -morpholine	84-98
323	Me	Cl	H	H	phenyl HCl.Salt	172-174
324	Me	Cl	H	H	4-Cl-phenyl	157.8-158.5
325	Me	Cl	H	H	3-Cl-phenyl	157.5-159
326	Me	Cl	H	H	4-SMe-phenyl	149-150
327	H	Me	Cl	H	$(\text{CH}_2)_2\text{OMe}$	172.4-174.2
328	H	Me	Cl	H	tetrahydro-furan-2-ylmethyl	150.1-150.8

5

and are named as follows:

314. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-ethyl-2-thiourea.

10

315. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-methyl-2-thiourea.

15

316. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-phenyl-2-thiourea.



317. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-cyclohexyl-2-thiourea.
318. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-(2-methoxy-ethyl)-2-thiourea.
319. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-(tetrahydro-furan-2-ylmethyl)-2-thiourea.
320. 1-{2-[5-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-[(methoxy-carbonyl)methyl]-2-thiourea.
321. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-cyclopropyl-2-thiourea.
322. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-[2-(morpholin-4-yl)ethyl]-2-thiourea.
323. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-phenyl-2-thiourea hydrochloride.
324. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-(4-chloro-phenyl)-2-thiourea.
325. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-(3-chloro-phenyl)-2-thiourea.
326. 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-(4-methyl-thiophenyl)-2-thiourea.
327. 1-{3-Chloro-2-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-(2-methoxyethyl)-2-thiourea.
328. 1-{3-Chloro-2-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-(tetra-hydrofuran-2-ylmethyl)-2-thiourea.

- XI. Compounds of formula I where  $R_1=R_3=Me$ ;  $R_4=R_5=R_{12}=R_{13}=R_{15}=R_{16}=R_{22}=H$ ;  $R_{14}=Cl$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (V); and  $R_{30}=NH^*C(O)R_{31}$ , are:

CPD#	$R_{31}$	M. Pt. °C
329	Me	194-195
330	H	166.6-167.7
331	$CH(NH_2)CH_3 \cdot 2HCl$	129-210 chiral (R)
332	morpholino	243-244

5

and are named as follows:

329. N-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}acetamide.
330. N-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}formamide.
331. (R)-N-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-alaninamide.
332. N-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-pyridin-5-yl}morpholin-4-ylcarboxamide.
- XII. Compounds of formula I where  $R_1=Me$ ;  $R_4=R_5=R_{13}=R_{15}=R_{16}=R_{22}=H$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (V); and  $R_{30}=NHH^*$  are:

CPD#	$R_3$	$R_{12}$	$R_{14}$	M. Pt. °C
333	Me	H	Cl	133.1-133.6
334	Me	H	SMe	152.6-153.7
335	H	Me	Me	238.9-240.2

and are named as:

333. {2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine.

334. {2-[5-(4-Methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine.

5

335. {2-[5-(2,4-Dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine.

Miscellaneous compounds:

- 10 I. Compounds of formula I where  $R_1=R_3=Me$ ;  $R_4=R_5=R_{13}=R_{22}=H$ ;  $R_{20}=$  is a group represented by formula (V); and  $R_{24}=R_{30}=NHSO_2R_{31}$  are:

CPD#	$R_{10}$	$R_{31}$	M. Pt. °C
336	2-thienyl	$CH_2CH_3 \cdot HCl$	166-167
337	2-thienyl	$Me \cdot HCl$	168-170.5

and are named as follows:

15

336. N-{2-[5-Thenoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}ethane-sulfonamide hydrochloride.

20

337. N-{2-[5-Thenoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}methane-sulfonamide hydrochloride.

- II. Compound of formula (I) where  $R_1=Me$ ;  $R_3=R_4=R_{12}=R_{13}=R_{15}=R_{16}=R_{24}=R_{25}=R_{26}=H$ ;  $R_{14}=Me$ ;  $R_{10}=$  is a group represented by formula (A);  $R_{20}=$  is a group represented by formula (U); and  $R_{23}=R_{30}=NH^*SO_2R_{31}$ , is:

25

CPD#	$R_5$	$R_{22}$	$R_{31}$	
338	H	H	Me	Foam

and is named as follows:

338. N-{3-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.

30

III. Compounds of formula I where  $R_1=Me$ ;  $R_4=R_5=R_{13}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH*SO_2R_{31}$ , are:

CPD#	$R_{10}$	$R_3$	$R_{22}$	$R_{31}$	M. Pt. °C
339	2-thienyl	H	H	Me	142-143
340	2-thienyl	Me	F	Me	169-170
341	3-pyridyl	Me	H	Me	130-132

5

and are named as follows:

339. N-{4-[5-(2-thenoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methanesulfonamide.

10 340. N-{3-Fluoro-4-[5-(2-thenoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.

341. N-{4-[5-(2-Nicotinyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}methane-sulfonamide.

15

IV. Compounds of formula(I) where  $R_1=Me$ ;  $R_4=R_5=R_{13}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}=NH*SO_2NR_{32}R_{34}$ , is:

CPD#	$R_{10}$	$R_3$	$R_{22}$	$R_{32}$	$R_{34}$	M. Pt. °C
342	2-thienyl	Me	F	H	H	204-205

20 and is named as follows:

342. 1-{3-Fluoro-4-[5-(2-thenoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.

- V. Compounds of formula I where  $R_4=R_5=R_{12}=R_{13}=R_{15}=R_{16}=R_{22}=R_{23}=R_{25}=R_{26}=H$ ;  $R_{10}$  is a group represented by formula (A);  $R_{20}$  is a group represented by formula (U); and  $R_{24}=R_{30}$  are:

CPD#	$R_1$	$R_3$	$R_{14}$	$R_{30}$	M. Pt
343	Me	Me	Cl	OH	
344	Me	Me	Cl	OSO <sub>2</sub> NMe <sub>2</sub>	
345	H	H	SMe	NHSO <sub>2</sub> Me	188.7-189

5

and are named as follows:

343. 4-{5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl}phenol,  
m/e= 340 (M+).
- 10 344. 1-N,N-dimethylaminosulfonyloxy-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]benzene, m/e = 446 (M+).
- 15 345. N-{4-[5-(4-Methylthiobenzoyl)-1H-pyrrol-2-ylmethyl]phenyl}methanesulfonamide.

Preferred compounds of this invention are those where:

- (1)  $R_1$ ,  $R_3$ ,  $R_4$ , and  $R_5$  are independently H or alkyl; more preferably H or Me; most preferably  $R_1$  is Me;  $R_3$  is H or Me; and  $R_4$  and  $R_5$  are H;
- (2)  $R_{10}$  is a group represented by formula (A);
- (3)  $R_{12}$  and  $R_{16}$  are independently H, alkyl, hydroxy, alkyloxy, cyano, or halo; more preferably H, Me, OH, OMe, F, or Cl; most preferably H, Me, or OMe;
- (4)  $R_{13}$  is H or alkyl; more preferably H or Me; most preferably H;
- 25 (5)  $R_{14}$  is H, halo, alkyl, dialkylamino, alkoxy, alkylthio, or cyano; more preferably H, Me, OMe, F, Cl, NMe<sub>2</sub>, or SMe; most preferably H, F, Cl, Me, or OMe;
- (6)  $R_{15}$  is H or halo; more preferably H or Cl; most preferably H;
- (7)  $R_{20}$  is a group represented by formula (U) or (V); preferably (U);
- (8) where  $R_{20}$  is a group represented by formula (U):
- 30  $R_{22}$  is H, halo, alkyl, cyano, or -CF<sub>3</sub>; more preferably H, F, Cl, or CN; most preferably F, Cl, or CN;

- $R_{23}$  and  $R_{25}$  are H;  
 $R_{24}$  is  $R_{30}$ ; and  
 $R_{26}$  is H, alkyl, or halo; more preferably H, Me, F, or Cl; most preferably H or F;  
 (9) where  $R_{20}$  is a group represented by the formula (V):  
 5  $R_{22}$  is preferably meta to  $R_{30}$  and is preferably H, F, Cl, or cyano; more preferably H, F, or Cl; most preferably H;  
 (10)  $R_{30}$  is  $-NHH^*$ ,  $-NH^*C(S)R_{32}R_{33}$ ,  $-NH^*SO_2R_{31}$ , or  $-NH^*SO_2NR_{32}R_{34}$ ; more preferably  
 $-NHH^*$ ,  $-NH^*SO_2R_{31}$ , or  $-NH^*SO_2NR_{32}R_{34}$ ; most preferably  $-NH^*SO_2R_{31}$  or  
 10  $-NH^*SO_2NR_{32}R_{34}$   
 (11)  $R_{31}$  is alkyl, 2-hydroxyethyl, 2,3-dihydroxypropyl, or  $-(CH_2)_nR_{35}$  where n is 2 or 3 and  $R_{35}$  is OMe, cycloamino,  $-NMe_2$ , or  $-CO_2R_{27}$  where  $R_{27}$  is alkyl; more preferably Me or 2-hydroxyethyl;  
 (12)  $R_{32}$  is H or Me; more preferably H;  
 15 (13)  $R_{34}$  is H, Me, 2-hydroxyethyl, or acetyl; more preferably H or Me; most preferably H;  
 and pharmaceutically acceptable salts thereof.

Exemplary particularly preferred compounds are:

- 20 N-{3-Cyano-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- N-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-  
 25 2-(hydroxy)ethanesulfonamide.
- N-{3-Fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-  
 2-(hydroxy)ethanesulfonamide.
- 30 N-{3-Fluoro-4-[5-(2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide.
- N-{3-Fluoro-4-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-  
 35 2-(hydroxy)ethanesulfonamide.

- 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.
- 5 1-{3-Fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-phenyl}sulfamide.
- 1-{3-Cyano-4-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-sulfamide.
- 10 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-methyl-2-thiourea
- N-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.
- 15 N-{3-Chloro-2-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}methanesulfonamide.
- 1-{2-[5-(4-Methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}sulfamide.
- 20 {2-[5-(4-Thiomethylbenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine.
- 25 4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenol.
- N-{2-[5-(4-Methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.
- 30 1-{3-Fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-phenyl}-sulfamide.
- N-{2-[5-(4-Methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.
- 35

N-{3,5-Difluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.

5 N-{3-Fluoro-4-[5-(2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.

N-{3-Fluoro-4-[5-(2-methyl-4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.

10 N-{3-Fluoro-4-[5-(2-chloro-4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methanesulfonamide.

15 N-{3-Fluoro-4-[5-(2-methoxy-4-methyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.

N-{3-fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.

20 Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis*, Volumes 1-15 (John Wiley and Sons, 1991); *Rodd's Chemistry of Carbon Compounds*, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); and *Organic Reactions*, Volumes 1-40 (John Wiley and Sons, 1991). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

35 The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.



Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78° C to about 150° C, more preferably from about 0° C to about 125° C and most preferably at about room (or ambient) temperature, e.g., about 20° C.

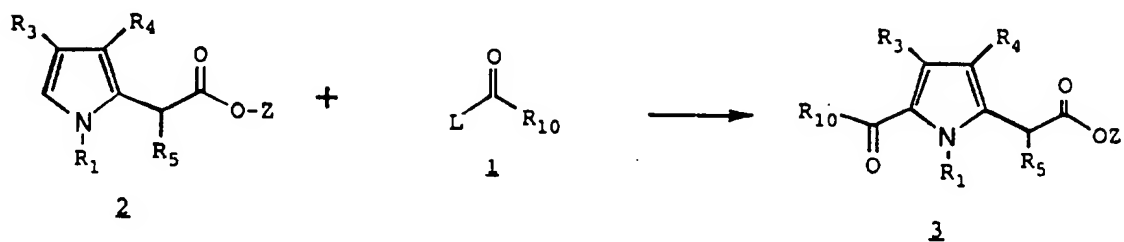
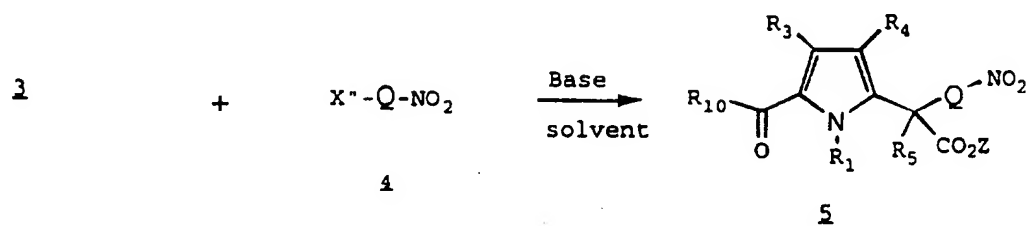
In general, compounds of formula I are prepared by modification of 5-arylpyrrol-2-ylmethylanilines ("anilines") or 5-arylpyrrol-2-ylmethylpyridinamines ("pyridinamines"). These anilines or pyridinamines, which will sometimes be referred to later as compounds of formula Ia, are compounds of formula I where R<sub>30</sub> is -NH<sub>2</sub>; so they are both compounds of this invention and are also intermediates to further compounds of this invention.

For convenience in the synthetic schemes following, R<sub>20</sub> (with the exception of the R<sub>30</sub> substituent thereon), will be denoted by -Q-. The use of -Q-R<sub>30</sub> to denote R<sub>20</sub> does not imply that R<sub>20</sub> is substituted only with R<sub>30</sub>; R<sub>20</sub> may contain any other substituents within the scope described in the Summary of the Invention (or as specifically limited in a particular reaction sequence).

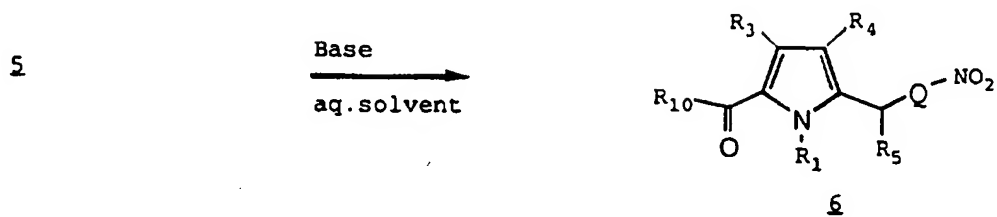
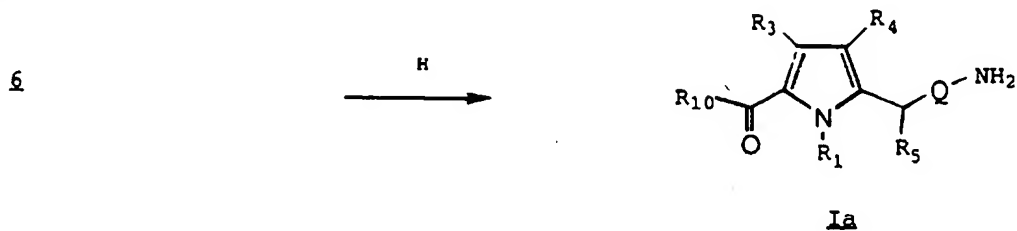
Schemes A, B, C and D describe alternative methods to generate the compounds of formula Ia.

Scheme A

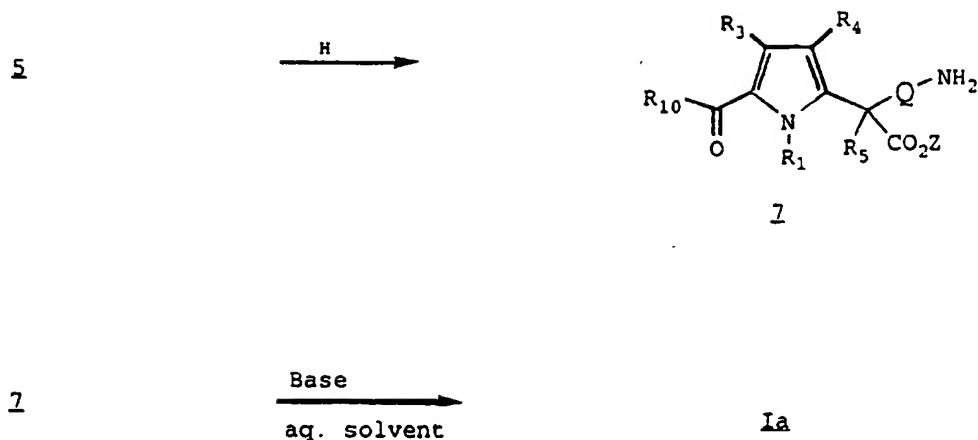
The aniline/pyridinamine of formula Ia can be prepared from a pyrrole-2-acetate 2 by the method shown in Scheme A.

Step 1:Step 2:

5

Step 3:Step 4:

- 59 -

Step 3.4 (alternate)

In Step 1, a 5-arylpyrrole-2-acetate  $\underline{3}$  is prepared by acylating a pyrrole-2-acetate  $\underline{2}$ , where  $R_1$  is not hydrogen and  $Z$  is alkyl (particularly Me or ethyl) with an acylating agent of formula  $\underline{1}$ , where  $R_{10}$  is as defined in the Summary of the Invention (except that  $R_{14}$  is not an amino or alkylamino group) and  $L$  is a leaving group under acylating conditions [such as halo (particularly Cl), dialkylamino (particularly -NMe<sub>2</sub>), or cycloamino (particularly morpholino)]. Suitable solvents for the reaction are halogenated and aromatic hydrocarbons (e.g. dichloroethane, xylenes and the like). When  $L$  is halo, the reaction proceeds on heating; when  $L$  is dialkylamino or cycloamino, the reaction proceeds in the presence of an acid halide such as phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride, and the like (a Vilsmeier-Haack reaction).

In general, the compounds of formula  $\underline{1}$ , the pyrrole-2-acetates  $\underline{2}$  and the 5-arylpyrrole-2-acetates  $\underline{3}$  are known to or can readily be synthesized by those of ordinary skill in the art. For example, synthesis of a pyrrole-2-acetate  $\underline{2}$ , where  $R_1$  and  $R_3$  are methyl is described by Stahley G.P., Marlett E.M., and Nelson G.E., *J. Org. Chem.*; 48:4423 (1983) and where  $R_1$  is hydrogen and  $R_5$  is H or alkyl is described by Schloemer G.C., et al., *J. Org. Chem.*; 59, 5230 (1994).

Also, a pyrrole-2-acetate  $\underline{2}$  where  $R_5$  is alkyl, can be prepared by reacting a pyrrole-2-acetate  $\underline{2}$  where  $R_5$  is hydrogen, with an alkylating agent  $R_5L$  where  $L$  is a leaving group under alkylating conditions, such as halo, methanesulfonate, p-toluenesulfonate and the like. The reaction is carried out in the presence of a base (e.g., cesium carbonate, sodium hydride, or potassium carbonate) in a suitable polar aprotic organic solvent such as ether,

THF, dioxane, DMF and the like. However, it is preferable to introduce R<sub>5</sub> as the alkyl group, in Step (2) of the synthesis as described below.

The 5-aroypyrrole-2-acetates **3**, where R<sub>1</sub> is alkyl and R<sub>3</sub> is methylthio or where R<sub>1</sub> and R<sub>5</sub> together form -(CH<sub>2</sub>)<sub>2</sub>-, and their synthesis are described in Muchowski, J. M.;  
5 Galeazzi, E., et al., *J. Med. Chem.* **32**, 1202-1207, (1989).

Certain 5-aroypyrrole-2-acetates **3** are also commercially available. For example the sodium salts of zomepirac, 5-(4-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetate and tolmetin, 5-(4-methyl-benzoyl)-1-methylpyrrole-2-acetate are available from Sigma Chemical Company.

10 If a compound of formula **3** is obtained as an acid or salt, it is converted to an alkyl (preferably Me or ethyl) or an allyl ester prior to Step 2. The allyl ester is preferred when -Q- in compound **5** contains an electron withdrawing group such as a halo group meta to the nitro group or a base sensitive group such as a cyano group as one of the substituents. The alkyl or allyl ester is prepared by reacting the alkali metal salt of compound **3** with an  
15 alkylating agent such as an alkyl (preferably Me or ethyl) or allyl halide (e.g., Cl or Br). Suitable solvents for the reaction are polar aprotic organic solvents. If compound **3** is obtained as an alkyl ester (e.g., Z = Me or ethyl) but the allyl ester is preferred, the alkyl ester is converted to the corresponding allyl ester by heating it in an excess of allyl alcohol, in the presence of a suitable basic catalyst such as titanium isopropoxide.

20 In Step 2, a 2-(5-aroypyrrol-2-yl)-2-(nitrophenyl/nitropyridyl)acetate **5** is prepared by nucleophilic substitution of X" in a nitro compound of formula **4**, where X" is a leaving group under arylation conditions (e.g., Cl, F, -OSO<sub>2</sub>Me, -OSO<sub>2</sub>CF<sub>3</sub>, and the like) by a 5-aroypyrrole-2-acetate **3**. The reaction is carried out in the presence of a strong base (e.g., sodium or potassium hydride, lithium diisopropylamide and the like) under an inert  
25 atmosphere (e.g., argon or nitrogen). Suitable solvents are aprotic organic solvents (e.g., tetrahydrofuran, dimethylformamide, and the like). Additionally, a compound of formula **5** where R<sub>5</sub> is alkyl, can be prepared from a compound of formula **3** where R<sub>5</sub> is hydrogen, by carrying out the above arylation procedure in the presence of an alkylating agent R<sub>5</sub>L, where L is a leaving group under alkylating condition.

30 Compounds of formula **4** are commercially available or can be synthesized by one of ordinary skill in the art.

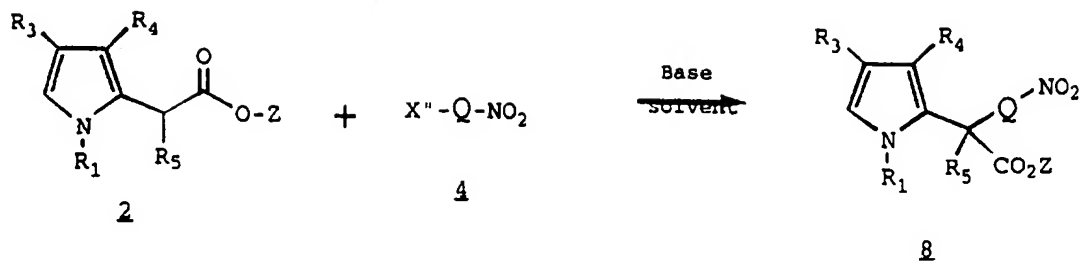
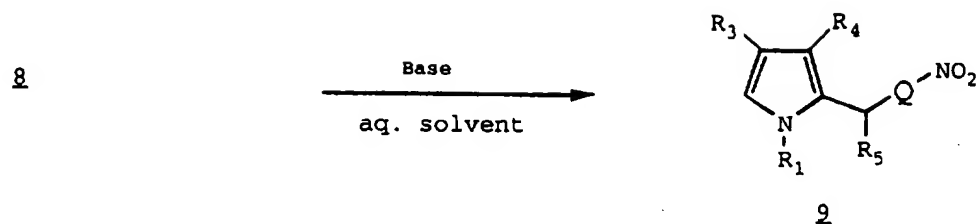
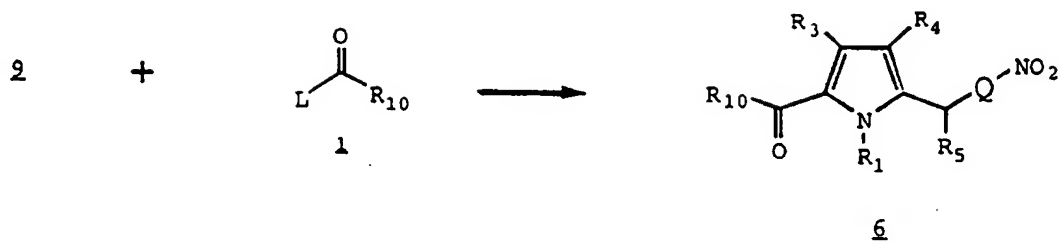
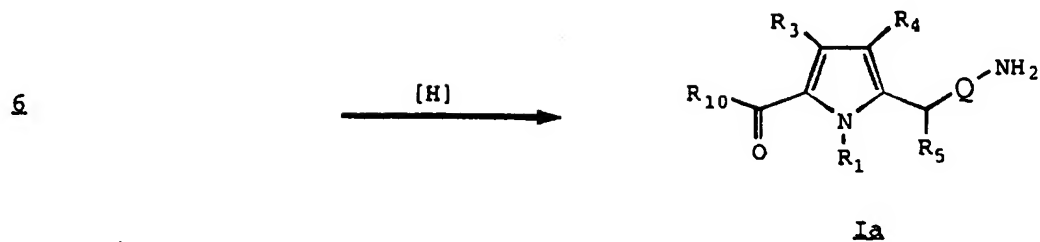
In Step 3, a nitrobenzene /nitropyridine 6 is prepared by hydrolysis and decarboxylation of the ester group in a compound of formula 5. If compound 5 is the alkyl ester, the hydrolysis /decarboxylation proceeds on heating, in the presence of an aqueous solution of a suitable base (e.g., LiOH, NaOH and the like) and in a suitable organic solvent such as methanol, methoxyethanol, DMF, THF, or mixtures thereof (preferably a high boiling solvent such as methoxyethanol or DMF). If the decarboxylation does not occur during the hydrolysis, it is effected by acidifying the reaction mixture with an aqueous acid such as HCl to give the free acid, which undergoes decarboxylation either at ambient temperature or upon heating in a high boiling organic solvent.

10 If compound 5 is the allyl ester, the deprotection reaction proceeds at ambient temperature, in the presence of a palladium catalyst (e.g., tetrakis(triphenylphosphine) palladium), an allyl scavenger (e.g., morpholine or pyrrolidine) and under an inert atmosphere. Suitable solvents for the reaction are polar organic solvents (e.g., THF, dioxane, or DMF).

15 In Step 4, an aniline/pyridinamine of formula Ia is prepared by reducing the nitro group of nitrobenzene/nitropyridine 6 to an amino group. Suitable nitro group reducing conditions include iron metal with ammonium chloride in ethanol/water, nickel boride in acidic methanol or catalytic hydrogenation using a platinum or palladium catalyst (e.g., PtO<sub>2</sub> or Pd/C) in an alcoholic solvent (e.g., methanol or ethanol, preferably ethanol).

20 Alternatively, a compound of formula Ia can be prepared from an alkyl ester of compound 5 by carrying out the reduction of the nitro group to the amino group, followed by the hydrolysis and decarboxylation of the ester group in the resulting aniline/pyridinamine-acetate of formula 7, utilizing the reaction conditions described in Steps 4 and 3 above. In general, this alternative route for the synthesis of compounds of formula Ia is preferred over the hydrolysis/decarboxylation, followed by reduction sequence described in steps 3 and 4 above when 5 is the alkyl ester.

The synthesis of a (5-aroypyrrol-2-ylmethyl)aniline and a [2-(5-aroypyrrol-2-ylmethyl)-pyridin-5-yl]amine utilizing the reaction conditions described in Scheme A is given in Examples 1-6.

Scheme BStep 1:Step 2:Step 3:Step 4:

The aniline/pyridinamine of formula Ia can also be prepared from a pyrrole-2-  
 5 acetate **2** by the method shown in Scheme B.

In Step 1, a 2-pyrrole-2-(nitrophenyl/nitropyridyl)acetate 8 is prepared by proceeding as in Step 2 of Scheme A but substituting a pyrrole-2-acetate 2 for a 5-  
aroylpyrrole-2-acetate 3.

5 In Step 2, a (pyrrol-2-ylmethyl)nitrobenzene/nitropyridine 9 is prepared by proceeding as in Step 3 of Scheme A but substituting a compound of formula 8 for a compound of formula 5.

10 In Step 3, a 2-(5-aroylpyrrol-2-ylmethyl)nitrobenzene/nitropyridine 6 is prepared from the compound of formula 9 by 5-acylation, utilizing the reaction conditions described in Step 1 of Scheme A.

In Step 4, an aniline/pyridinamine Ia is prepared by reduction of the nitro group in compound 6, utilizing the reaction conditions described in Step 4 of Scheme A.

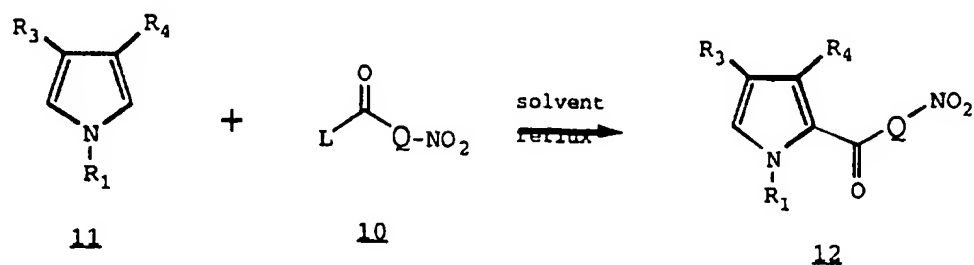
15

Although Scheme B is generally suitable for synthesis of compounds of formula I that are within the scope of this invention, it is particularly suitable for the preparation of compounds of formula I where R<sub>14</sub> is an amino or alkylamino group. A detailed description of the synthesis of a compound of formula Ia by this method is given in Example 7.

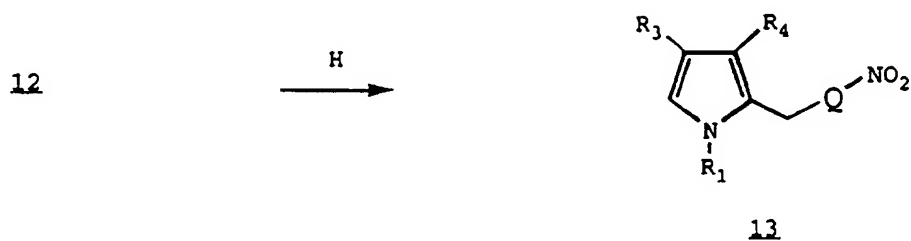
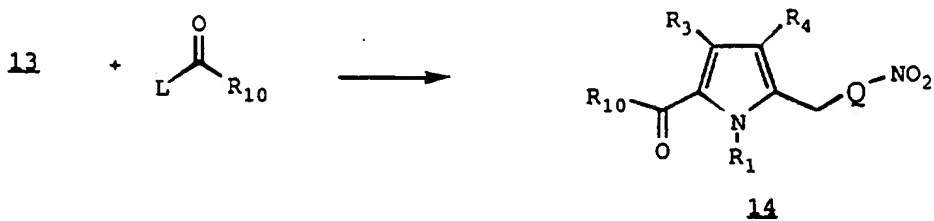
20

Scheme C

The aniline/pyridinamine of formula Ia where  $R_1$  is H or alkyl and  $R_5$  is hydrogen, can also be prepared starting from a pyrrole as shown in Scheme C.

Step 1:

$R_1 = H$  or alkyl

Step 2:Step 3:Step 4:



In Step 1, a 2-(nitroaroyl)pyrrole 12 is prepared by proceeding as in Step 1 of Scheme A but substituting an acylating agent of formula 10 and a pyrrole of formula 11 for the compounds of formula 1 and 2 respectively.

- 5            In Step 2, a (pyrrol-2-ylmethyl)nitrobenzene/nitropyridine 13 is prepared by reduction of the ketone group in compound 12 with a reducing agent selective for the ketone group, such as sodium cyanoborohydride in presence of a catalyst such as zinc iodide. Suitable solvents for this reaction include dihalogenated solvents (e.g., dichloromethane or dichloroethane).

10

A compound of formula Ia is then prepared from the compound of formula 13 by 5-acylation, followed by nitro group reduction in steps (3) and (4), utilizing the reaction conditions described in Steps 1 and 4 of Scheme A.

- 15            This route is particularly suited for preparing compounds of formula I where  $R_{20}$  is a group represented by the formula (U) in which  $R_{23}$  or  $R_{25}$  is  $R_{30}$ .  
A detailed description of the synthesis of a compound of formula Ia by this method is given in Example 8.

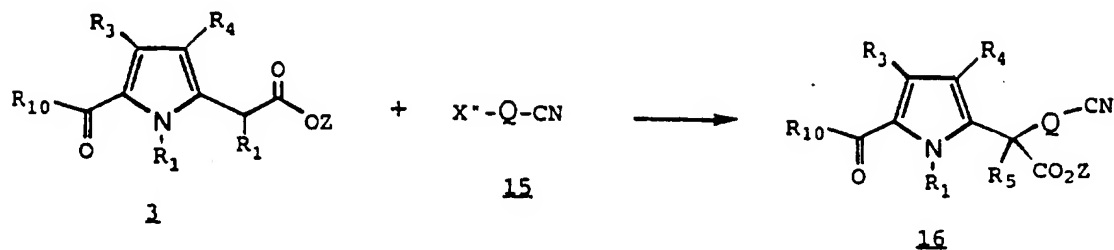
- 66 -

Scheme D

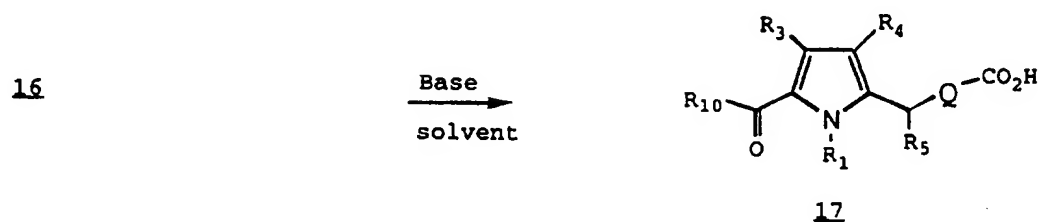
The aniline/pyridinamine of formula Ia can also be prepared by the method shown in

Scheme D.

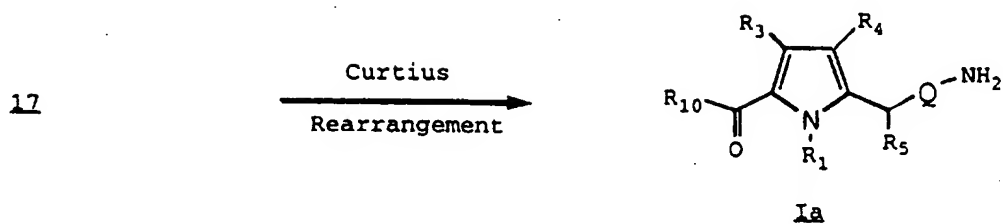
Step 1:



Step 2:



Step 3:



5

In Step 1, a 2-(5-arylpyrrol-2-yl)-2-(cyanophenyl/cyanopyridyl)acetate 16 is prepared by proceeding as in Step 2 of Scheme A but substituting a nitrile of formula 15 for a nitro compound of formula 4.

10

In Step 2, a (5-arylpyrrol-2-ylmethyl)benzoic/nicotinic acid 17 is prepared by proceeding as in Step 3 of Scheme A but substituting the compound of formula 16 for a compound of formula 5.

The hydrolysis/ decarboxylation reaction condition also causes the hydrolysis of the nitrile group.

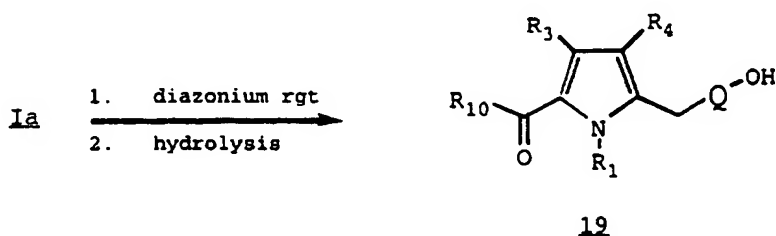
In step 3, a compound of formula Ia is then prepared from a compound of formula 17, using a Curtius rearrangement reaction. Suitable conditions are those described in Yamada F., et al.; *J. Am. Chem. Soc.*; 6203, (1974) and Yamada F., et al.; *Tetrahedron*, 30, 2151 (1974).

The preparation of a compound of formula Ia by this method is described in Example 9.

Schemes E - I describe methods to prepare other compounds of formula I from compounds of formula Ia.

#### Scheme E

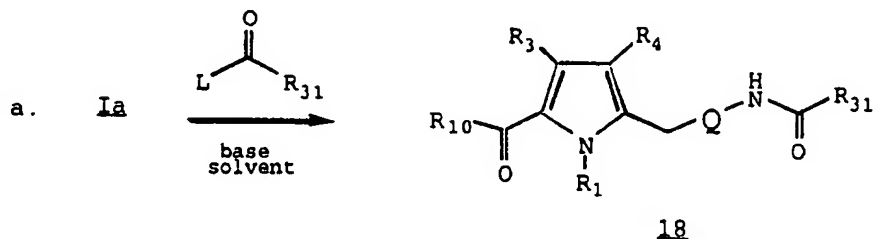
Scheme E describes the synthesis of compounds of formula I where  $R_{30}$  is OH:



A compound of formula I where  $R_{30}$  is -OH can be prepared by converting an aniline/pyridinamine of formula Ia to a diazonium salt, which upon hydrolysis in an aqueous acid gives the hydroxy group. The diazonium salt is prepared by reacting a compound of formula Ia with a nitrite salt (e.g.,  $\text{NaNO}_2$ ,  $\text{KNO}_2$  and the like) in an aqueous solvent (e.g., water, aqueous acetic acid, aqueous organic mixtures such as acetic acid/acetone) or an alkyl nitrite such as isoamyl nitrite in a non-aqueous solvent such as glacial acetic acid, acetone or a mixture thereof. The conversion of a compound of formula Ia to a compound of formula I where  $R_{24} = R_{30}$  is -OH is described in detail in Example 10.

Scheme F

Scheme F describes the synthesis of compounds of formula I where  $R_{30}$  is  $-\text{NHC}(\text{O})\text{R}_{31}$ :



5

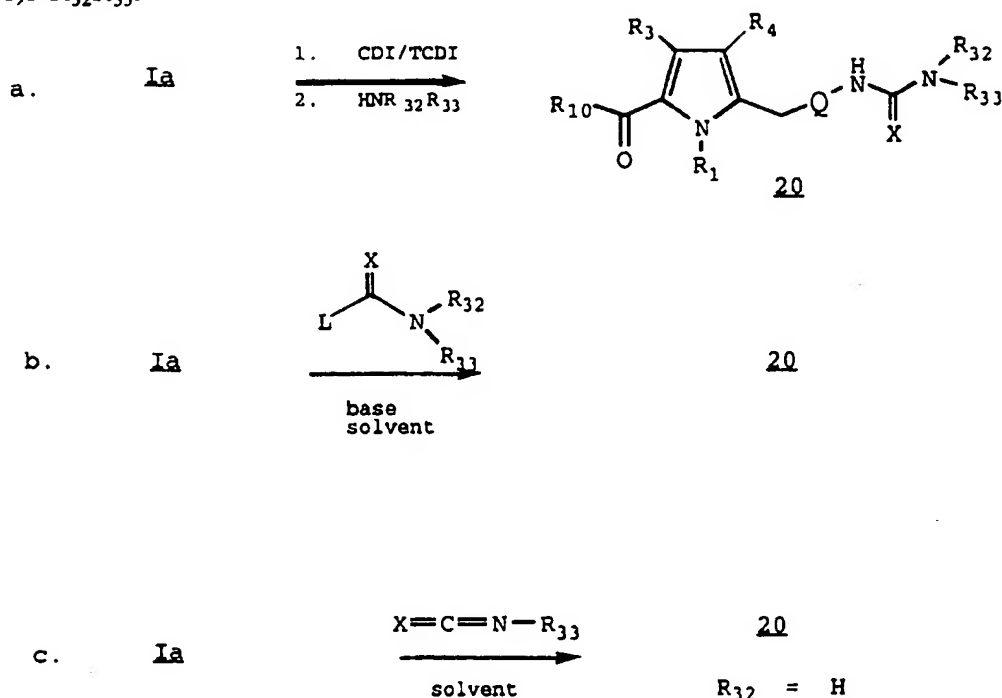
A compound of formula I where  $R_{30}$  is an amide group can be prepared, either:

- (a) by reacting an aniline/pyridinamine of formula Ia with an acylating reagent  $\text{R}_{31}\text{COL}$ , where L is a leaving group under acylating conditions, such as a halo (particularly Cl or Br) or imidazolide. Suitable solvents for the reaction include aprotic polar solvents (e.g., dichloromethane, THF, dioxane and the like.) When an acyl halide is used as the acylating agent the reaction is carried out in the presence of a non-nucleophilic organic base (e.g., triethylamine or pyridine, preferably pyridine); or
- (b) by heating a compound of formula Ia with an acid anhydride. Suitable solvents for the reaction are THF, dioxane and the like. Detailed descriptions of the conversion of a compound of formula Ia to compounds of Formula I where  $R_{31}$  is  $-\text{NHC}(\text{O})\text{CH}_3$  or  $-\text{NHCHO}$  are given in Examples 11 and 12.

15

Scheme G

Scheme G describes the synthesis of compounds of formula where  $R_{30}$  is  $-NHC(X)NR_{32}R_{33}$ :



5

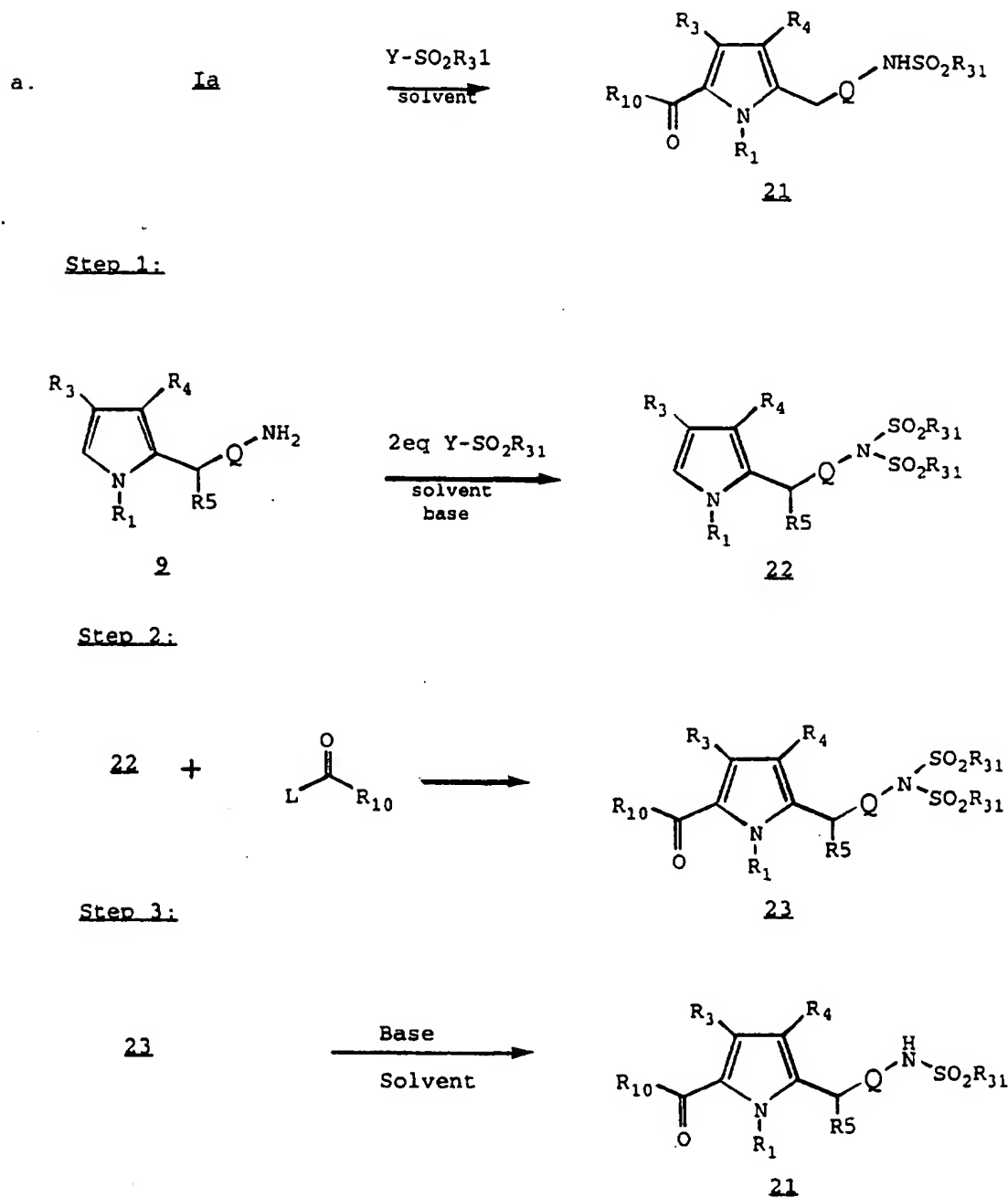
A compound of formula I where  $R_{30}$  is a urea/thiourea group can be prepared, either:

- 10 (a) by reacting an aniline/pyridinamine of formula Ia with an activating agent such as carbonyl diimidazole/ thiocarbonyl diimidazole, followed by nucleophilic displacement of the imidazole group with a primary or secondary amine. The reaction occurs at ambient temperature. Suitable solvents include polar organic solvents (e.g., THF, dioxane and the like);
- 15 (b) by reacting a compound of formula Ia with a carbamoyl/thiocarbamoyl halide. The reaction is carried out in the presence of a non-nucleophilic organic base. Suitable solvents for the reaction are dichloromethane, 1,2-dichloroethane, THF, or pyridine; or
- 20 (c) by reacting a compound of formula Ia with an isocyanate/isothiocyanate in an aprotic organic solvent (e.g., benzene, THF, DMF and the like). Detailed descriptions of the conversion of a compound of formula Ia to compounds of formula I where  $R_{30}$  is

-NHC(O)NHCH<sub>2</sub>CH<sub>2</sub>OH, -NHC(O)NMe<sub>2</sub>, -NHC(O)NHMe, or -NHC(S)NHMe are given in Examples 13-16.

### Scheme H

5 Scheme H is used to synthesize compounds of formula I where R<sub>30</sub> is -NHSO<sub>2</sub>R<sub>31</sub>:

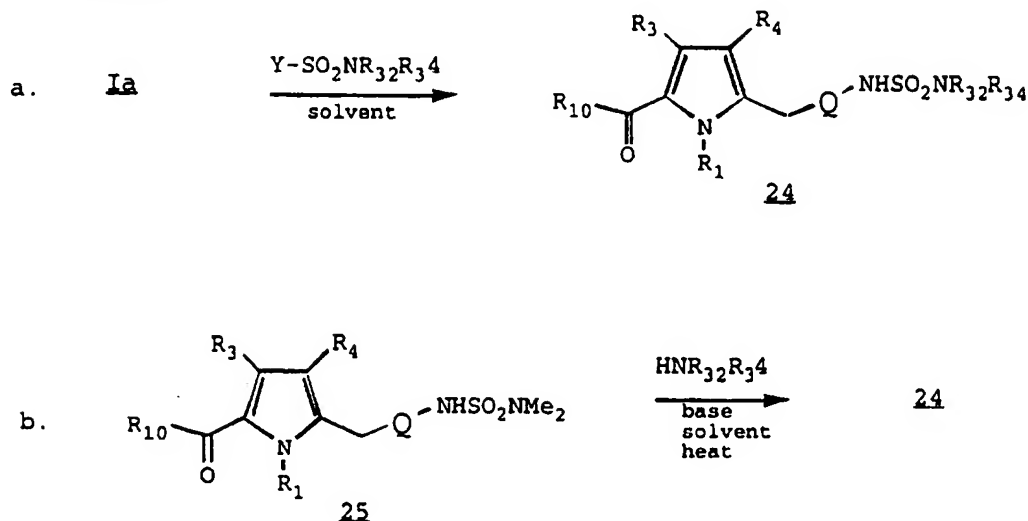


A compound of formula I where  $R_{30}$  is a sulfonamide group can be prepared, either:

- (a) by reacting an aniline/pyridinamine of formula Ia with a sulfonyl halide, utilizing the reaction conditions described in method (b) of Scheme G. Sulfonyl halides are commercially available or may be prepared by methods such as those described in (1) Langer, R. F.; *Can. J. Chem.*; **61**, 1583-1592, (1983); (2) Aveta, R.; et. al.; *Gazetta Chimica Italiana*, **116**, 649-652, (1986); (3) King, J. F. and Hillhouse, J. H.; *Can. J. Chem.*; **54**, 498, (1976); and (4) Szymonifka, M. J. and Heck, J. V.; *Tet. Lett.*; **30**, 2869-2872, (1989). Detailed descriptions of the conversion of a compound of formula Ia to compounds of formula I where  $R_{30}$  is  $-NHSO_2Me$ ,  $-NHSO_2(CH_2)_2OH$ ,  $-NHSO_2CH=CH_2$ , or  $-NHSO_2(CH_2)_2NMe_2$  are given in Examples 17 -20.
- (b) by reacting a compound of formula 2 with two equivalents of a sulfonyl halide in the presence of a non-nucleophilic organic base to give a bis-sulfonamide. Suitable solvents for the reaction are halogenated organic solvents (e.g., dichloromethane, dichloroethane,  $CCl_4$  and the like). The resulting bis-sulfonamide is 5-acylated under the reaction conditions described in Step 1 of Scheme A. Hydrolysis of one of the sulfonyl groups in presence of an inorganic base (e.g., LiOH, KOH and the like) gives a compound of formula I. Suitable solvents for the hydrolysis include THF, dioxane, DMF, and the like. A detailed description of the conversion of a compound of formula Ia to a compound of formula I, where  $R_{30}$  is  $-NHSO_2Me$  by this procedure is given in Example 21.

Scheme I

Scheme I was used to prepare compounds of formula I where  $R_{30}$  is  $-\text{NHSO}_2\text{NR}_{32}\text{R}_{34}$  :



5

A compound of formula I where  $R_{30}$  is a sulfamide group can be prepared, either:

(a) by reacting an aniline/pyridinamine of formula Ia with a sulfamoyl halide, utilizing the reaction conditions described in method (b) of Scheme G. Sulfamoyl halides are commercially available or may be prepared by methods such as those described in Graf, R.; *German Patent*, 931225 (1952) and Catt, J.D. and Matler, W.L.; *J. Org. Chem.*, **39**, 566-568, (1974); or

(b) by an amine exchange reaction, in which a dimethyl sulfamide (prepared according to the method described above) is heated with an amine  $\text{NHR}_{32}\text{R}_{34}$  in an aromatic hydrocarbon in presence of an excess amount of a non-nucleophilic organic base. Detailed descriptions of the conversion of a compound of formula Ia to a compound of formula I where  $R_{30}$  is  $-\text{NHSO}_2\text{NMe}_2$ ,  $-\text{NHSO}_2\text{NH}_2$ , or  $-\text{NHSO}_2$ -morpholine are given in Examples 22-24.

20

Compounds of formula I and Ia having a group that would be unstable under the reaction conditions utilized in Schemes A-I can be prepared by the modification of another group present on a corresponding compound of formula I and Ia, e.g.; compounds of formula I containing a hydroxy group may be prepared by de-alkylation/benzylation of an alkyloxy/benzyloxy substituent; those containing an acid group, by hydrolysis of an ester



group; and those containing a cyano, by displacement of a bromine atom on the corresponding compounds of formula I. Similarly, a compound of formula Ia having an alkenyl or alkynyl group can be prepared by reacting a corresponding compound of formula Ia containing a bromine or iodine atom with trimethylsilylacetylene under the Castro-  
5 Stephens reaction conditions. A detailed description of the conversion of a benzyloxy group to a hydroxy group; an ester group to an acid and a bromine atom to a cyano group are given in Examples 25-27 respectively. Furthermore, a compound of formula I and Ia can prepared by substitution of a group present on a corresponding compound of formula I and Ia, e.g., a compound of formula Ia where  $R_{14}$  is H, or alkylthio may be conveniently  
10 prepared by dehalogenation/ substitution of a chlorine atom on a corresponding compound of formula Ia. The conversion of a compound of formula Ia where  $R_{14}$  is chloro to a corresponding compound of formula Ia where  $R_{14}$  is H or methylthio is described in Examples 28 and 29 respectively.

15 The compounds of the invention are inhibitors of prostaglandin G/H Synthase I and II (COX I and COX II), especially COX II, *in vitro*, and as such possess both anti-inflammatory and analgesic properties *in vivo*. See, for example, Goodman and Gilman's "The Pharmacological Basis of Therapeutics", Ninth Edition, McGraw Hill, New York, 1996, Chapter 27. The compounds, and compositions containing them, are therefore useful  
20 as anti-inflammatory and analgesic agents in mammals, especially humans in the treatment of inflammation and pain caused by diseases such as arthritis, gout, and autoimmune disorders (such as systemic lupus erythematosus, rheumatoid arthritis, and type I diabetes).

As inhibitors of prostaglandin G/H Synthase, the compounds of this invention are  
25 also expected to be useful in the prevention and treatment of cancer, in particular colon cancer. It has been shown that COX-2 gene expression is upregulated in human colorectal cancers and that drugs that inhibit prostaglandin G/H Synthase are effective in animal models of cancer (Eberhart, C.E., et. al.; *Gastroenterology*, (1994), **107**, 1183-1188 and Ara, G., and Teicher, B.A., *Prostaglandins, Leukotrienes and Essential Fatty Acids*,  
30 (1996), **54**, 3-16). In addition, there is epidemiological evidence that shows a correlation between use of drugs that inhibit prostaglandin G/H synthase and a reduced risk of developing colorectal cancer, (Heath, C.W. Jr., et. al.; *Cancer*, (1994), **74**, No. 10, 2885-8).

35 The compounds of this invention are also expected to be useful in the prevention and treatment of Alzheimer's disease. Indomethacin, an inhibitor of prostaglandin G/H

synthase, has been shown to inhibit the cognitive decline of Alzheimer's patients. (Rogers, J., et. al., *Neurology*, (1993), **43**, 1609). Also, the use of drugs which inhibit prostaglandin G/H synthase has been linked epidemiologically with a delayed onset of Alzheimer's disease, (Breitner, J.C.S., et. al., *Neurobiology of Aging*, (1995), **16**, No. 4, 523 and *Neurology*, (1994), **44**, 2073).

The anti-inflammatory activity of the compounds of this invention may be assayed by measuring the ability of the compound to inhibit COX I and COX II, especially COX II, *in vitro*, using a radiometric assay, as described in more detail in Example 31. It may also be assayed by *in vivo* assays such as the Rat Carrageenan Paw, and Rat Air-Pouch assays, as described in more detail in Examples 32 and 33. The analgesic activity of the compounds of this invention may be assayed by *in vivo* assays such as the Acetic Acid induced Rat Writhing Assay, and the rat arthritis pain model, as described in more detail in Example 34.

In general, the compounds of this invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of this invention, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

Therapeutically effective amounts of compounds of formula I may range from approximately 0.1-75 mg per Kilogram body weight of the recipient per day; preferably about 5-20 mg/Kg/day. Thus, for administration to a 70 Kg person, the dosage range would most preferably be about 350 mg to 1.4 g per day.

In general, compounds of this invention will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions and are comprised of, in general, a compound of formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients

are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of formula I. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art .

5

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

Other suitable pharmaceutical excipients and their formulations are described in *Remington's Pharmaceutical Sciences*, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

20

The level of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt%) basis, from about 0.01-99.99 wt% of a compound of formula I based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1-80 wt%. Representative pharmaceutical formulations containing a compound of formula I are described in Example 30.

The following preparations and examples explain the invention further.

30

### EXAMPLE 1

#### Synthesis of 3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-yl]methylaniline

a) Ethyl 1,4-dimethylpyrrole-2-acetate (37.0 g, 0.19 mol), benzoyl chloride (54.3 g, 0.38 mol), and triethylamine (52.9 ml, 0.38 mol) were dissolved in xylenes (750 ml), and

35

the reaction mixture was refluxed for 18 h under argon. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. Purification on a Florisil<sup>®</sup> column (hexane followed by hexane-ethyl acetate, 4:1) gave ethyl 5-benzoyl-1,4-dimethylpyrrole-2-acetate (30.45 g, 57%) as a solid.

5

b) Ethyl 5-benzoyl-1,4-dimethylpyrrole-2-acetate (5.0 g, 17.5 mmol) [prepared as in Example 1, Step (a)], was dissolved in DMF (50 ml) and the solution was cooled in an ice bath to 0 °C under an argon atmosphere. Sodium hydride, 50% /mineral oil, (1.3 g, 27.1 mmol) was added, and after 5 min 3,4-difluoronitrobenzene (3.36 g, 21.1 mmol) was added to the reaction mixture. After 1 h the reaction mixture was poured into 10% HCl/ice and the product was extracted into ethyl acetate. The organic phase was washed with water, dried over sodium sulfate, and evaporated to dryness. Purification on a Florisil<sup>®</sup> column (hexane-ethyl acetate, 9:1) gave ethyl 2-(5-benzoyl-1,4-di-methylpyrrol-2-yl)-2-(2-fluoro-4-nitrophenyl)acetate (6.22 g, 84%) as a solid.

15

c) A mixture of ethyl 2-(5-benzoyl-1,4-dimethylpyrrol-2-yl)-2-(2-fluoro-4-nitrophenyl)-acetate (6.0 g, 14.1 mmol) [ prepared as in Example 1, Step (b) ], nickel boride (8.0 g, 62.4 mmol), hydrochloric acid (50 ml, 1M) and methanol (150 ml) was heated at reflux for 1 h. The reaction mixture was cooled and filtered through Celite<sup>®</sup>. After removing the methanol *in vacuo*, the resulting aqueous mixture was made basic with ammonium hydroxide, and the product was extracted into ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. Evaporation of the organic layer gave ethyl 2-(5-benzoyl-1,4-dimethyl-pyrrol-2-yl)-2-(2-fluoro-4-aminophenyl)acetate (5.3 g, 95%).

25

d) Ethyl 2-(5-benzoyl-1,4-dimethylpyrrol-2-yl)-2-(2-fluoro-4-aminophenyl)acetate (5.3 g, 13.4 mmol) [prepared as in Example 1, Step (c)] and 50% aqueous NaOH (5 ml) were dissolved in a 1:1 mixture of methanol/THF (100 ml), and the reaction mixture was refluxed for 30 min. After removing the solvents *in vacuo*, the residue was diluted with water and acidified with concentrated HCl. The product was extracted into ethyl acetate, and the organic layer was washed with brine, dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was re-dissolved in DMF (200 ml) and refluxed for 30 min. The reaction mixture was cooled, poured into water/ice, and the product was extracted into ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline (3.12 g, 69%) as a solid.

35

## EXAMPLE 2

### Synthesis of 4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline

- 5 a) Ethyl 2-(5-benzoyl-1,4-dimethylpyrrol-2-yl)-2-(4-nitrophenyl)acetate (8.2 g, 20.2 mmol) [prepared by proceeding as described in Example 1, Steps (a) and (b) ] was dissolved in a 1:1 mixture of methanol/THF (200 ml). An aqueous solution of LiOH (250 ml, 0.4M, 100.9 mmol) was added and the mixture was stirred at 60 °C for 2 h. The  
10 organic solvents were evaporated *in vacuo*, the aqueous residue was acidified with 10% HCl, and the product was extracted into ethyl acetate. The organic phase was washed with water, dried over sodium sulfate, and concentrated under vacuum. Purification on a Florisil® column (hexane-ethyl acetate, 4:1) gave 4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]-nitrobenzene (6.68 g, 99%) as a yellow solid.
- 15 b) To a slurry of 4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]nitrobenzene (3.55 g, 10.6 mmol) [prepared as in Example 2, Step (a) ] in methanol (170 ml) and hydrochloric acid (50 ml, 1M) was added nickel boride (3.41 g, 26.6 mmol), and the mixture was stirred at 75 °C for 15 h. The reaction mixture was cooled, basified with ammonium hydroxide and  
20 the product was extracted into ethyl acetate. The organic phase was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline (3.11 g, 96%) as a pale yellow solid.

## EXAMPLE 3

### Synthesis of 4-[1-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]ethyl]aniline

- 25 a) The methyl ester of zomepirac (6.12 g, 20.0 mmol) and 4-fluoronitrobenzene (2.65 ml, 25.0 mmol) were dissolved in DMF (65 ml) and sodium hydride, 60%/in mineral oil  
30 (1.68 g, 42 mmol) was added at room temperature. After 30 min methyl iodide (3.12 ml, 50 mmol) was added to the reaction mixture and the stirring was continued for an additional 15 min. The reaction mixture was poured into a mixture of 1N sodium bisulfate (20 ml) and ice-water and stirred overnight. The resulting solid was filtered and washed with water. Recrystallization from ethyl acetate-hexane gave methyl 2-[5-(4-chlorobenzoyl)-1,4-di-  
35 methylpyrrol-2-yl]-2-(4-nitro-phenyl)-2-methylacetate (7.85 g, 89%) as a solid, mp 180.9-181.7 °C.

- b) 4-{1-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]ethyl}aniline can be prepared from methyl 2-{5-(4-chlorobenzoyl)-1,4-dimethylpyrrol-2-yl}-2-(4-nitrophenyl)-2-methyl-acetate by proceeding as in Example 1, Steps (c) and (d) or Example 2, Steps (a) and (b).

#### EXAMPLE 4

##### Synthesis of 3-chloro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline

10

- a) The sodium salt of tolmetin (15.0 g, 47.6 mmol) and allyl bromide (4.3 ml, 49.9 mmol) were dissolved in DMF (50 ml) and the mixture was stirred at room temperature until the esterification was complete (~30h). The solvent was removed *in vacuo* and the residue was partitioned between ether and water. The organic layer was separated, washed with water, 1M sodium hydroxide, and brine, and dried over sodium sulfate. Evaporation gave allyl 5-(4-methylbenzoyl)-1-methylpyrrole-2-acetate (11.97 g, 85%) as a solid.

- b) Allyl 5-(4-methylbenzoyl)-1-methylpyrrole-2-acetate (11.83 g, 39.8 mmol) [prepared as in Example 4, Step (a)] and 3,4-dichloronitrobenzene (7.64 g, 39.8 mmol) were dissolved in dry DMF (50 ml). The reaction mixture was cooled under nitrogen to 0 °C and sodium hydride powder (2.01 g, 83.5 mmol) was added in portions. After stirring at 0° C for 30 min, the reaction mixture was warmed to room temperature and quenched with 1M HCl. The product was extracted into ether and the organic layer was washed with water and brine and dried over magnesium sulfate. Evaporation gave allyl 2-[(5-(4-methylbenzoyl)-1-methylpyrrol-2-yl)-2-(2-chloro-4-nitrophenyl)-acetate (17.15 g, 98%) as a foam.

- c) Allyl 2-[(5-(4-methylbenzoyl)-1-methylpyrrol-2-yl)-2-(2-chloro-4-nitrophenyl)acetate (17.15 g, 39.2 mmol [ prepared as in Example 4, Step (b)]) was dissolved in THF (100 ml) under nitrogen. Morpholine (34.2 ml, 391.7 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (45 mg, 0.04 mmol) were added and the reaction mixture, which developed a white precipitate, was stirred for 20 min. The solvent was removed *in vacuo* and the residue was dissolved in ether. The ether layer was separated and washed with 1M sodium bisulfate and brine, and dried over magnesium sulfate. Evaporation gave 3-chloro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-yl-methyl]nitro-benzene (14.38 g, 99%) as a yellow oil.

- d) 3-Chloro-4-{5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl}nitrobenzene (14.38 g, 39.0 mmol) [prepared as in Example 4, Step (c)] was dissolved in ethanol (300 ml) and an aqueous solution of ammonium chloride (14.0 g in 150 ml) and iron powder (14.0 g) were added to the solution. The reaction mixture was refluxed for 30 min, then cooled to room temperature and filtered. The filtrate was concentrated, diluted with water, and extracted with ether and methylene chloride. The organic layer were combined, washed with brine and dried over sodium sulfate. Evaporation gave 3-chloro-4-{5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl}aniline (12.09 g, 92%) as a yellow solid.

10

### EXAMPLE 5

#### Synthesis of {2-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine

- a) A solution of tolmetin methyl ester (30.0 g, 0.11 mol) and 2-chloro-5-nitropyridine (21.9 g, 0.138 mol) in DMF (350 ml) was cooled to 4 °C and sodium hydride powder (5.87 g, 0.23 mol) was added in portions. The reaction was stirred for 1.5 h and then poured into a cold aqueous solution of potassium bisulfate (31.0 g in 1500 ml water). The resulting orange precipitate was filtered, washed with water, dried under vacuum, and then stirred with ethyl acetate (500 ml). Filtration gave methyl 2-[(5-(4-methylbenzoyl)-1-methylpyrrol-2-yl)-2-(5-nitropyridin-2-yl)- acetate (23g) as an orange solid, mp 162.5-163.8 °C
- b) Methyl 2-[(5-(4-methylbenzoyl)-1-methylpyrrol-2-yl)-2-(5-nitropyridin-2-yl)acetate (34.0 g, 86.4 mmol) [prepared as described in Example 5, Step (a)] was dissolved in a mixture of ethanol/ THF (600 ml/ 200ml) and subjected to catalytic hydrogenation over PtO<sub>2</sub> (0.7 g) in a Parr shaker apparatus at 30 psi for 4 h. The reaction mixture was filtered through Celite<sup>®</sup> and the filtrate was concentrated to dryness. Purification by flash chromatography (hexane-ethyl acetate) gave methyl 2-[(5-(4-methylbenzoyl)-1-methylpyrrol-2-yl)-2-(5-aminopyridin-2-yl)-acetate (22.0 g, 70%) as a dark orange gum.
- c) To a solution of methyl 2-[(5-(4-methylbenzoyl)-1-methylpyrrol-2-yl)-2-(5-aminopyridin-2-yl)acetate (22.0 g, 60.5 mmol) [prepared as in Example 5, Step (b)] in methanol (400 ml) was added an aqueous solution of sodium hydroxide (5.8 g, 145.0 mmol) in 60 ml water. The dark brown reaction mixture was stirred overnight under argon, then acidified with 3 N HCl to pH 2.5 and stirred an additional 6 h. The reaction mixture was

then neutralized with a saturated solution of sodium bicarbonate to pH 7.5. The resulting brown precipitate was filtered and purified by flash chromatography (hexane-ethyl acetate) to yield a solid. Recrystallization from hexane-ethyl acetate gave {2-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-pyridin-5-yl}amine (10.2 g, 55%) as a light brown solid,  
5 mp 104-106.6 °C.

### EXAMPLE 6

#### Synthesis of 4-[5-(2,4-Dimethylbenzoyl)-1-methylpyrrol-2-ylmethyl]aniline

10

a) To a suspension of 2,4-dimethylbenzoic acid (10 g, 66.59 mmol) in ethyl acetate (100 ml) was added oxalyl chloride (5.81 ml, 66.59 mmol), and the mixture was slowly heated to 40°C. After 1.5 h, the solvents were removed *in vacuo*, and the product 2,4-dimethylbenzoyl chloride was used in the next step without purification.

15

b) To a solution of 2,4-dimethylbenzoyl chloride (66.59 mmol) [prepared as described in Example 6, Step (a)] in cumene (150 ml) was added methyl 1-methylpyrrole-2-acetate (8 ml, 55.56 mmol) and lithium carbonate (6.16 g, 83.34 mmol), and the reaction mixture was heated to reflux. After 1.5 h, the reaction mixture was cooled to ambient temperature  
20 and the solvent was removed *in vacuo*. Purification by column chromatography (ethyl acetate-hexanes) gave methyl 2-[5-(2,4-dimethylbenzoyl)-1-methylpyrrole-2-acetate (4.03 g, 25%), as a waxy solid.

c) Methyl 2-[5-(2,4-dimethylbenzoyl)-1-methylpyrrole-2-acetate (2.75 g, 9.64 mmol)  
25 [prepared as described in Example 6, Step (b)] and 3,4-difluoronitrobenzene (1.28 ml, 11.56 mmol) were dissolved in anhydrous DMF (15 ml) and NaH (486 mg, 20.24 mmol) was added in portions at 0°C. The reaction mixture was stirred at 0°C for 2 h, then quenched with 1N NaHSO<sub>4</sub>, and partitioned between ether and 1N NaHSO<sub>4</sub>. The organic layer was separated, dried over magnesium sulfate, and concentrated to dryness.  
30 Purification by column chromatography (ethyl acetate/hexane) gave methyl 2-[5-(2,4-dimethylbenzoyl)-1-methyl-pyrrol-2-yl)-2-(2-fluoro-4-nitrophenyl)acetate (3.56 g, 87%) as a pale yellow oil.

d) To a solution of methyl 2-[5-(2,4-dimethylbenzoyl)-1-methylpyrrol-2-yl)-2-(2-fluoro-4-nitrophenyl)acetate (3.51 g, 8.27 mmol) [prepared as described in Example 6,  
35 Step(c)] in 75 ml allyl alcohol was added titanium tetrakisopropoxide (0.244 ml, 0.827



mmol), and the reaction mixture was heated to reflux. After 36 h, the reaction mixture was cooled to room temperature, and partitioned between ether and water. The organic layer was separated, dried over magnesium sulfate, and concentrated to dryness to give allyl 2-[5-(2,4-dimethylbenzoyl)-1-methylpyrrol-2-yl]-2-(2-fluoro-4-nitrophenyl)- acetate (3.60 g, 97%) as a pale yellow oil.

e) To a solution of allyl 2-[5-(2,4-dimethylbenzoyl)-1-methylpyrrol-2-yl]-2-(2-fluoro-4-nitrophenyl)acetate (3.6 g, 7.99 mmol) [prepared as described in Example 6, Step (d)] in anhydrous THF (40 ml) was added morpholine (6.99 ml, 79.90 mmol) and tetrakis-(triphenylphosphine) palladium (9 mg, 0.008 mmol). After 1.5 h, the solvent was evaporated and the residue was partitioned between ether and 1N NaHSO<sub>4</sub>. The organic layer was separated, dried over magnesium sulfate, and concentrated to dryness. Purification by column chromatography (ethyl acetate/hexane) gave 4-[5-(2,4-dimethylbenzoyl)-1-methyl-pyrrol-2-yl-methyl]nitrobenzene (2.73 g, 93%) as a pale yellow oil.

f) 4-[5-(2,4-Dimethylbenzoyl)-1-methylpyrrol-2-ylmethyl]nitrobenzene (923 mg, 2.52 mmol) [prepared as described in Example 6, Step(e)], was dissolved in ethyl acetate (10 ml). 10% Pd/C (92 mg) was added, and the reaction mixture was vigorously stirred under hydrogen atmosphere at ambient temperature and atmospheric pressure for 2 h. The mixture was filtered through Celite', and the filtrate was evaporated to dryness to give 4-[5-(2,4-dimethylbenzoyl)-1-methylpyrrol-2-yl-methyl]aniline (718 mg, 85%) as pale yellow crystals, mp 107.6-108.5° C.

25

### EXAMPLE 7

#### Synthesis of 4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline

a) Methyl 1-methylpyrrole-2-acetate (5.0 g, 32.0 mmol) and 4-chloronitrobenzene (10.3 g, 65.0 mmol) were dissolved in DMF (30 ml) and the mixture was cooled in an ice bath under argon. Sodium hydride, 50% in mineral oil, (3.1 g, 64.0 mmol) was added in portions. After stirring for 1 h at room temperature the reaction mixture was poured into 1M HCl/ice and the product was extracted into ethyl acetate. The organic extracts were washed with water, dried over sodium sulfate, and concentrated to dryness. Purification on a Florisil® column (methylene chloride) gave methyl 2-(1-methylpyrrol-2-yl)-2-(4-nitrophenyl)acetate (4.13 g, 46%) as a solid.

- b) Methyl 2-(1-methylpyrrol-2-yl)-2-(4-nitrophenyl)acetate (3.8 g, 14.0 mmol) [prepared as in Example 7, Step (a)] was dissolved in a 1:1 mixture of MeOH-THF (100 ml) and cooled in an ice bath under argon. A solution of 0.4 M lithium hydroxide (69 ml) was added and the reaction mixture was stirred at room temperature. After 2 h, the reaction mixture was poured into 1 M HCl/ice and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and concentrated under reduced pressure. The solid residue was redissolved in DMF (40 ml) and heated at reflux. After 20 min the reaction mixture was poured into ice/water and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and concentrated to dryness. Purification on a Florisil<sup>®</sup> column (hexane-ethyl acetate, 9:1) gave 4-(1-methylpyrrol-2-yl-methyl)nitrobenzene (2.53 g, 82%) as a solid.
- c) 4-(1-Methylpyrrol-2-ylmethyl)nitrobenzene (1.2 g, 5.5 mmol) [prepared as in Example 7, Step (b)], 2,4-dimethylbenzoyl chloride (1.6 g, 9.5 mmol), and triethylamine (1.3 ml, 9.3 mmol) were dissolved in xylenes (50 ml), and the reaction mixture was heated at reflux under argon. After 48 h, the reaction mixture was passed through a Florisil<sup>®</sup> column (hexane followed by hexane-ethyl acetate, 95:5) to give 4-{5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-yl-methyl}nitrobenzene (0.81 g, 42%) as a solid.
- d) A mixture of 4-{5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl}-nitrobenzene (0.81 g, 2.3 mmol), [prepared as in Example 7, Step (c)], nickel boride (1.6 g), 1M HCl (30 ml), and methanol (30 ml) was refluxed for 30 min. The reaction mixture was filtered through a pad of Celite<sup>®</sup> and the filter cake was washed with ethyl acetate. The filtrate was cooled, made basic with concentrated ammonium hydroxide, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to give 4-{5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl}aniline (760 mg, 100%) as an oil.

EXAMPLE 8

- a) A solution of 1-methylpyrrole (10.0 g, 123.0 mmol), 3-nitrobenzoyl chloride (68.47 g, 369 mmol), and triethylamine (17.14 ml, 123 mmol) in xylenes (150 ml) was  
5 refluxed for 40 h. Purification of the reaction mixture on a Florisil<sup>®</sup> column (hexane-acetone, 85:15) gave 2-(3-nitrobenzoyl)-1-methylpyrrole (13.0 g, 46%) as a solid.
- b) A mixture of 2-(3-nitrobenzoyl)-1-methylpyrrole (5.0 g, 21.7 mmol) [prepared as  
in Example 8, Step (a)], zinc iodide (10.38 g, 32.5 mmol), sodium cyanoborohydride  
10 (10.22 g, 162.7 mmol), and 1,2-dichloroethane (300 ml) was refluxed for 16 h. The  
reaction mixture was cooled to room temperature, filtered through Celite<sup>®</sup>, and then  
concentrated to dryness. Purification of the residue on a Florisil<sup>®</sup> column (hexane-acetone,  
98:1) gave 3-(1-methylpyrrol-2-ylmethyl)nitrobenzene (3.55 g, 75%) as a solid.
- 15 c) 3-(1-Methylpyrrol-2-ylmethyl)nitrobenzene (2.0 g, 9.2 mmol) [prepared as in  
Example 8, Step (b)], 4-methylbenzoyl chloride (2.84 g, 18.4 mmol), and triethylamine  
(2.0 ml, 14.3 mmol) were dissolved in xylenes (80 ml) and the reaction mixture was  
refluxed for 36 h. Purification on a Florisil column (hexane-ethyl acetate, 95:5) gave 3-{5-  
(4-methyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl}nitrobenzene (0.86 g, 28%) as a solid.  
20
- d) A mixture of 3-{5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl}-nitro-  
benzene (0.86 g, 2.6 mmol) [prepared as in Example 8, Step (c)], nickel boride (1.0 g),  
10% HCl (13 ml), and methanol (35 ml) was heated at 65 °C for 40 min. The reaction  
mixture was cooled to room temperature, made basic with concentrated ammonium  
25 hydroxide, and filtered through Celite<sup>®</sup>. The product was extracted into ethyl acetate, and  
the organic extracts were washed with water and brine, and dried over sodium sulfate.  
Evaporation of the organics gave 3-{5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-yl-  
methyl}aniline (0.73 g, 99%) as a solid.

EXAMPLE 9Synthesis of 3,5-Difluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline

5

a) The ethyl ester of zomepirac (4.66g, 15.2 mmol) and 3,4,5-trifluorobenzonitrile (3.23g, 20.6 mmol) were dissolved in DMF (75 ml) and NaH (60% in mineral oil, 1.28g, 32.0 mmol) was added in portions under an argon atmosphere. The reaction mixture was heated at 60°C for 2.5 h, then cooled to room temperature and added slowly to a mixture of  
10 ice/water (600 ml) containing 6N HCl (7.5 ml). The product was filtered and dried under vacuum. Recrystallization from ethyl acetate-hexane gave ethyl 2-[5-(4-chlorobenzoyl)-1,4-dimethyl-pyrrol-2-yl]-2-(2,6-difluoro-4-cyanophenyl)acetate (5.67 g, 84% yield) as yellow crystals, mp 155-155.5°C.

15 b) To a slurry of ethyl 2-[5-(4-chlorobenzoyl)-1,4-dimethylpyrrol-2-yl]-2-(2,6-difluoro-4-cyanophenyl)acetate (0.05g, 0.11 mmol) [prepared as described in Example 9, Step (a)] in methoxyethanol (4 ml) was added an aqueous solution of lithium hydroxide monohydrate (0.02g in 0.5 ml H<sub>2</sub>O), and the reaction mixture was heated at reflux under an argon atmosphere. After 24 hr, the reaction mixture was cooled to room temperature and  
20 poured into a mixture of ice/water (40 ml) containing 1N HCl (1 ml). The solid was filtered to give crude {4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]benzoic acid (0.037g) as a tan solid. Flash chromatography on a silica gel column (0.5% acetic acid-30% acetone: hexane), followed by recrystallization from methanol-acetone gave pure {4-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]benzoic acid (0.032g,  
25 70.2% yield) as a white solid, mp 245-246.8°C.

c) Phosphoryl azide (1.0 ml, 4.61 mmol) was added to a mixture of {4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]benzoic acid (1.49g, 3.69 mmol) [prepared as described in Example 9, Step (b)], and triethylamine (0.77 ml, 5.54 mmol) in toluene at  
30 0° C under a nitrogen atmosphere. After stirring at room temperature for 10 min, the reaction mixture was heated to 100° C over the course of 1 hr. After heating at 100°C for 1 h, the reaction mixture was cooled to room temperature and trimethylsilylethanol (1.06 ml, 7.38 mmol) was added. The reaction mixture was reheated and maintained at 50°C for 1 h under a nitrogen atmosphere, and then the solvent was removed by evaporation under  
35 reduced pressure. The resulting yellow oil was redissolved in THF (100 ml) and tetrabutylammonium fluoride (10 ml, 1M soln. in THF) was added. After heating the

reaction mixture at reflux for 3 h the solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate and water. The organic extracts were washed with water, dried over magnesium sulfate, and evaporated to give a yellow oil. Purification by chromatography on a silica gel column (25% ethyl acetate:hexane), followed by  
5 recrystallization from acetone-hexane gave 3,5-difluoro-4-{5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl}aniline (0.64g, 64.4% yield) as white crystals, mp 208.2-210°C.

#### EXAMPLE 10

10

##### Synthesis of 4-{5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl}phenol

4-{5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl}aniline (1.36 g, 4.0 mmol) [prepared by the method described in Example 1, but substituting zomepirac methyl  
15 ester and 4-fluoronitrobenzene for ethyl 5-benzoyl-1,4-dimethylpyrrole-2-acetate and 3,4-difluoro-nitrobenzene respectively, in Step (b)], was dissolved in acetic acid (20 ml), and a solution of 1N sulfuric acid in acetic acid (4.4 ml), followed by acetone (12.5 ml) was added. The reaction mixture was cooled to 6 °C and isoamyl nitrite (0.65 ml, 4.8 mmol) was added. After 1.5 h, the mixture was poured into ether and stored at 2 °C for 6 h. The  
20 purple precipitate was filtered, washed with ether and then suspended in acetone (50 ml). After adding sulfuric acid (20 ml, 0.1N), the reaction mixture was stirred at 60 °C for 3 h and then diluted with ethyl acetate and water. The organic layer was separated and washed with water, and dried over sodium sulfate. The solvent was removed *in vacuo* to give a deep red residue (0.8 g). Purification by flash chromatography (hexane-ether, 6:4),  
25 followed by recrystallization from hexane-acetone gave 4-{5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl}phenol (213 mg, 16%) as a solid, mp 183.4-185.1 °C

EXAMPLE 11Synthesis of N-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]pyridin-5-yl}acetamide.

5

A solution of N-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine (0.3 g, 0.88 mmol) [prepared by the method described in Example 5, but substituting zomepirac methyl ester for tolmetin methyl ester in Step (a)] and acetic anhydride (0.375 ml, 3.96 mmol) in THF was stirred at 60 °C for 4 h. The solvents were removed under reduced pressure and the residue was crystallized from hexane-chloroform to give N-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-acetamide (295 mg, 88%) as a solid, mp 194-195 °C.

15

EXAMPLE 12Synthesis of N-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]pyridin-5-yl}formamide

20

The mixed anhydride of formic and acetic acid was prepared by adding formic acid (1 ml, 98%) dropwise to acetic anhydride (2 ml) and heating the mixture at 55 °C for 2.5 h. This reagent (2.2 ml) was then added to a solution of N-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]-pyridin-5-yl}amine (0.3 g, 0.88 mmol) in THF (7 ml), and the reaction mixture was heated overnight at 60 °C. The solvents were removed *in vacuo* and the residue was crystallized from chloroform-hexane to give N-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}formamide (175 mg, 54%) as a solid, mp 166.6-167.7 °C

25

EXAMPLE 13

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Synthesis of 1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]phenyl}-3-(2-hydroxyethyl)urea

4-{5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl}aniline (0.33 g, 0.98 mmol) and 1,1'-carbonyldiimidazole (0.4 g, 2.46 mmol) were dissolved in DMF, and the reaction mixture was stirred at room temperature for 1 h. Ethanolamine (0.3 ml, 4.91

35

mmol) was added and after 1.5 h the mixture was diluted with water. The product was extracted into ethyl acetate, and the organic layer was dried over  $\text{MgSO}_4$  and then concentrated under vacuum. Purification by flash chromatography (ethyl acetate), followed by recrystallization from hexane-chloroform gave 1-{4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-(2-hydroxyethyl)urea (239 mg, 57%) as a solid, mp 209.6-210.2 °C.

#### EXAMPLE 14

##### 10        Synthesis of 1-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]pyridin-5-yl}-3,3-dimethylurea

15        {2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl} amine [prepared by the method described in Example 5, but substituting the methyl ester of zomepirac for the methyl ester of tolmetin in Step (a)] (0.45 g, 1.32 mmol) and dimethylcarbamoyl chloride (0.13 ml, 1.46 mmol) were dissolved in pyridine (6.6 ml), and the mixture was stirred at room temperature for 96 h. The solvents were removed *in vacuo* and the residue was crystallized from chloroform-hexane mixture to give 1-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3,3-dimethylurea (0.31 g, 57%) as a solid, mp 227.2-230.0 °C.

#### EXAMPLE 15

##### 25        Synthesis of 1-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]pyridin-5-yl}-3-methylurea

30        {2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl} amine (0.3 g, 0.88 mmol) was dissolved in THF (4 ml), and the solution was cooled to 0 °C. Methyl isocyanate (0.062 ml, 1.06 mmol) was added and the reaction mixture was stirred overnight at ambient temperature. Additional methyl isocyanate (0.062 ml) was added and the mixture was stirred for an additional 24 h. The reaction mixture was concentrated under vacuum and the residue was crystallized from hexane-chloroform to give 1-{2-[5-(4-chlorobenzoyl)-1,4-di-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-methylurea (240 mg, 69%), mp 234.0-235.5 °C.

EXAMPLE 16Synthesis of 1-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]pyridin-5-yl}-3-methyl-2-thiourea

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N-{2-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine

(0.3 g, 0.88 mmol) and methylisothiocyanate (0.3 ml, 4.4 mmol) were dissolved in THF and the reaction mixture was stirred at 60 °C overnight. The mixture was diluted with ethyl acetate and washed with 1N HCl, 10% sodium bicarbonate, water, and brine. The solvents  
10 were removed *in vacuo* and the crude product was purified by flash chromatography (ethyl acetate-methanol, 97:3) to give 1-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-3-methyl-2-thiourea (265 mg, 73%) as a solid, mp 135 °C.

15

EXAMPLE 17Synthesis of N-{3-Fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-yl-methyl]phenyl}methanesulfonamide

20 a) 3-Fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline (1.0 g, 3.1 mmol) [prepared as described in Example 1] was dissolved in pyridine (10 ml) and the solution was cooled to -5 °C. Methanesulfonyl chloride (0.39 g, 3.4 mmol) was added and after 1 h the reaction mixture was poured into 1M HCl/ice/water and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and  
25 concentrated to dryness. The residue was crystallized from methylene chloride-methanol to give N-{3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide (775 mg, 62%) as a solid, mp 165-167 °C.

b) Proceeding as described in Example 17, but substituting 3-Cyano-4-[5-(4-chloro-  
30 benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline [prepared by the method described in Example 4, but substituting the sodium salt of zomepirac for the sodium salt of tolmetin in Step (a) and 3-cyano-4-chloronitrobenzene for 3,4-dichloronitrobenzene in Step (b)], for 3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline gave N-{3-cyano-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}methanesulfonamide.

35



- c) Proceeding as described in Example 17, but substituting {2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine, [prepared by the method described in Example 5, but substituting the zomepirac methyl ester for the tolmetin methyl ester in Step (a)], for 3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline gave  
5 N-{2-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}methanesulfonamide.
- d) Proceeding as described in Example 17, but substituting {2-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine, [prepared by the method described in  
10 Example 5], for 3-Fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline gave N-{2-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-methanesulfonamide.
- e) Proceeding as described in Example 17, but substituting 3-fluoro-4-[5-(2-methoxy-  
15 benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline [prepared by the method described in Example 1, but substituting 2-methoxybenzoyl chloride and methyl 1-methylpyrrole-2-acetate for benzoyl chloride and ethyl 1,4-dimethylpyrrole-2-acetate, respectively in Step (a)] for 3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-yl-methyl]aniline gave N-{3-fluoro-4-[5-(2-methoxybenzoyl)-1-methyl-1H-pyrrol-2-yl-methyl]phenyl}-  
20 methanesulfonamide.
- f) Proceeding as described in Example 17, but substituting {3-chloro-2-[5-(4-methoxy-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine [prepared by the method described in Example 4, but substituting methyl 5-(4-methoxybenzoyl)-1,4-  
25 dimethylpyrrole-2-acetate for the sodium salt of tolmetin in step (a) and 2,3-dichloro-4-nitropyridine for 3,4-dichloronitrobenzene in Step (b)], for 3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline gave N-{3-chloro-2-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]pyridin-5-yl}methanesulfonamide.
- g) Proceeding as described in Example 17, but substituting {2-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine [prepared by the method described in Example 5, but substituting the methyl ester of tolmetin for methyl 5-(4-methylbenzoyl)-  
30 1-methylpyrrole-2-acetate in Step (b)], for 3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline gave N-{2-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}methanesulfonamide.

EXAMPLE 18Synthesis of N-{3-fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-yl-  
methyl]phenyl}-2-(hydroxy)ethanesulfonamide

- 5
- a) 3-Fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]aniline (0.75 g, 2.43 mmol) [prepared as described in Example 1, but substituting ethyl 1,4-dimethylpyrrole-2-acetate with methyl 1-methylpyrrole-2-acetate in Step (a)], and pyridine (0.39 ml, 4.88 mmol)
- 10 were dissolved in methylene chloride (8 ml). 2-Acetoxyethanesulfonyl chloride (681 mg, 3.65 mmol) was added to the solution and after 15 min, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated to dryness. Purification of the residue by flash chromatography (hexane-ethyl acetate, 3:2) gave N-{3-fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]-phenyl}-2-(acetoxy)ethanesulfonamide, (643 mg, 58%) as a solid.
- 15
- b) N-{3-Fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(acetoxy)-ethanesulfonamide (0.415 g, 0.905 mmol) [prepared as in Example 18, Step (a)] was dissolved in methanol (5 ml) and a 2.0 M solution of ammonia in methanol (4.53 ml, 9.05 mmol) was added. The mixture was stirred for 60 h, after which it was concentrated to dryness. Purification of the residue by flash chromatography gave N-{3-fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide (282 mg, 75%) as a solid.
- 20
- c) Proceeding as described in Example 18, but substituting 3-fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline [prepared by the method described in Example 6], for 3-fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]aniline gave N-{3-fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
- 25
- 30
- d) Proceeding as described in Example 18, but substituting 3-fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline [prepared by the method described in Example 1, but substituting the methyl ester of tolmetin for ethyl 5-benzoyl-1,4-dimethylpyrrole-2-acetate in step (b)], for 3-fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]aniline gave N-{3-fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.
- 35

- e) Proceeding as described in Example 18, but substituting 3-fluoro-4-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline [prepared by the method described in Example 1, but substituting 4-methoxybenzoyl chloride for benzoyl chloride in step (a)],  
5 for 3-fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]aniline gave N-{3-fluoro-4-[5-(4-methoxybenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)-ethanesulfonamide.

#### EXAMPLE 19

10 Synthesis of N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}ethanesulfonamide

- 4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline (1.1 g, 3.25 mmol) was dissolved in pyridine (16.5 ml) and 2-chloroethanesulfonyl chloride (1.02 ml,  
15 9.74 mmol) was added to the solution. The mixture was stirred for 1.5 h and then concentrated to dryness. The residue was filtered through a pad of silica gel (ethyl acetate) to give N-{4-[5-(4-chloro-benzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}ethanesulfonamide, (1.29 g, 93%) as a solid.

20 EXAMPLE 20

Synthesis of N-{4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(dimethylamino)ethanesulfonamide hydrochloride

- 25 N-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-ethanesulfonamide (250 mg, 0.583 mmol) [prepared as in Example 19], was dissolved in DMF (1.1 ml). Triethylamine (0.11 ml, 0.8 mmol), followed by dimethylamine hydrochloride (36 mg, 0.69 mmol), was added and the reaction mixture was stirred for 1 h. A second batch of trimethylamine and dimethylamine hydrochloride was added and the  
30 stirring was continued overnight. The reaction mixture was partitioned between ethyl acetate and water, and the organic layer was separated and dried over sodium sulfate. The solvent was removed *in vacuo* and the crude product was then dissolved in ethyl acetate, after which ethanolic HCl was added to give N-{4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(dimethyl-amino)ethanesulfonamide (257 mg, 86%) as the  
35 hydrochloride salt.

EXAMPLE 21Synthesis of N-{4-[5-(4-aminobenzoyl)-1-methyl-1H-pyrrol-2-yl]-methyl}phenyl}methanesulfonamide

- 5
- a) Methyl 1-methylpyrrole-2-acetate (5.32 g, 34.73 mmol) and 4-fluoro-nitrobenzene (4.9 g, 34.73 mmol) were dissolved in dry DMF (100 ml), and the solution was cooled to 0 °C under nitrogen. Sodium hydride powder (1.75 g, 72.93 mmol) was added in portions. After 30 min the reaction mixture was quenched with 1 M HCl and the product was
- 10 extracted into ether. The organic extracts were washed with water and brine, and dried over magnesium sulfate. The solvent was removed *in vacuo* to give methyl-2-(1-methylpyrrol-2-yl)-2-(4-nitrophenyl)acetate (9.20 g, 97%) as a red oil.
- b) Methyl 2-(1-methylpyrrol-2-yl)-2-(4-nitrophenyl)acetate (9.2 g, 33.54 mmol)
- 15 [prepared as in Example 21, Step (a)], was dissolved in methanol (100 ml) and an aqueous solution of lithium hydroxide (3.52 g in 50 ml of water) was added. After 1.5 h the reaction mixture was concentrated to dryness *in vacuo* and the resulting residue was dissolved in water (100 ml). The solution was acidified to pH 1 with 6 M HCl and then extracted with ethyl acetate. The organic extracts were washed with water, and brine, and dried over
- 20 magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (hexane-ethyl acetate, 9:1) to give 4-(1-methylpyrrol-2-ylmethyl)nitrobenzene (4.8 g, 66%) as a yellow oil.
- c) 4-(1-Methylpyrrol-2-ylmethyl)nitrobenzene (500 mg, 2.31 mmol) [prepared as
- 25 described in Example 21, Step (b)], was dissolved in ethyl acetate and subjected to hydrogenation over 5% Pd/C (50 mg) at ambient temperature and atmospheric pressure. After 3 h the mixture was filtered and the filtrate was concentrated to give 4-(1-methylpyrrol-2-yl-methyl)aniline (430 mg, 100%) as a yellow oil.
- d) A mixture of 4-(1-methylpyrrol-2-ylmethyl)aniline (3.21 g, 17.23 mmol) [ prepared
- 30 as in Example 21, Step (c)], and triethylamine (8.4 ml, 60.27 mmol) was cooled to 0 °C under nitrogen. Methanesulfonyl chloride (4.2 ml, 54.26 mmol) was added and after for 1.5 h the reaction mixture was diluted with methylene chloride. The organic layer was separated and washed with 1 M aqueous sodium bisulfate, and brine and then dried over
- 35 magnesium sulfate. Evaporation gave N-{4-(1-methylpyrrol-2-ylmethyl)phenyl}-

bismethanesulfonamide (6.63 g) as an orange foam which was used in step (e) without further purification.

5 e) N,N-dimethyl-4-nitrobenzamide (0.65 mg, 3.36 mmol) and phosphorus oxychloride were stirred together until the mixture became homogeneous. A solution of N-{4-(1-methylpyrrol-2-ylmethyl)-phenyl}-bis-methanesulfonamide (1.15 g) [prepared as described in Example 21, Step (d)], in dry dichloroethane (15 ml) was added and the stirring was continued overnight. Sodium bicarbonate (17 ml, 10% solution in water) was added and after 1.5 h the reaction mixture was cooled to room temperature, and diluted with  
10 methylene chloride. The organic layer was separated and washed with water and brine, and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (hexane-ethyl acetate, 3:2) to give N-{4-[5-(4-nitrobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-phenyl}bismethanesulfonamide (0.35 g, 25%) as an oil.

15 f) 4-{5-[(4-Nitrobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}bismethanesulfonamide (0.35 g, 0.712 mmol) [prepared as in Example 21, Step (e)], was dissolved in dioxane (4 ml) and an aqueous solution of lithium hydroxide (60 mg, 1.42 mmol in 1 ml of water) was added. After stirring for 60 h the mixture was partitioned between ethyl acetate  
20 and a 1M sodium bisulfate solution. The organic layer was separated, washed with brine, and dried over sodium sulfate. Concentration gave N-{4-[5-(4-nitrobenzoyl)-1-methyl-1H-pyrrol-2-yl-methyl]phenyl}methanesulfonamide (294 mg) as a dark yellow oil which was used in the next step without further purification.

25 g) N-{4-[5-[(4-Nitrobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl]methanesulfonamide (294 mg) [prepared as in Example 21, Step (f)], and an aqueous solution of ammonium chloride (0.3 g/ 2.5 ml water) were dissolved in ethanol (5 ml). Iron powder (0.2 g) was added and the reaction mixture was heated at reflux for 20 min. The mixture was filtered and the filter cake was washed with methylene chloride. The filtrate was diluted  
30 with ethyl acetate, washed with water, and brine, and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (hexane-ethyl acetate, 3:2). Recrystallization of the product from hexane-ethyl acetate gave N-{4-[5-(4-aminobenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}methanesulfonamide (175 mg, 64%) as a yellow powder.

EXAMPLE 22Synthesis of 1-{3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-yl-methyl]phenyl}-3,3-dimethylsulfamide

- 5 a) 3-Fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline (1.0 g, 3.1 mmol) [prepared by the method described in Example 1], and N,N-dimethylsulfamoyl chloride (894 mg, 6.2 mmol) were dissolved in pyridine (10 ml) and stirred at 50 °C for 12 h. The reaction mixture was poured into 1M HCl/ice/water and extracted with ethyl acetate.
- 10 The organic layer was separated, washed with water, dried over sodium sulfate and concentrated to dryness. The residue was triturated with methanol, filtered and then purified by preparatory thin layer chromatography TLC (hexane-ethyl acetate, 3:2). Crystallization from a chloroform-hexane mixture gave 1-{3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-yl-methyl]phenyl}-3,3-dimethylsulfamide (343 mg, 26%), mp 182-182 °C.
- 15 b) Proceeding as described in Example 22, but substituting 4-[5-(4-chlorobenzoyl)-1,4-di-methyl-1H-pyrrol-2-ylmethyl]aniline [prepared by the method described in Example 1, but substituting methyl ester of zomepirac and 4-fluoronitrobenzene for ethyl 5-benzoyl-1,4-di-methylpyrrole-2-acetate and 3,4-difluoronitrobenzene respectively in Step (b)], for
- 20 3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline gave 1-{4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide.

EXAMPLE 23

25 Synthesis of 1-{3-Fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-yl-methyl]phenyl}sulfamide

- a) A 1M solution of aminosulfamoyl chloride was prepared by addition of a solution of water (1.44 g, 80.0 mmol) in ethylene glycol dimethyl ether (20 ml) to a solution of
- 30 chlorosulfonyl isocyanate (7.0 ml, 80.0 mmol) in ethylene glycol dimethyl ether (60 ml) under nitrogen at -45 °C. The reaction mixture was allowed to warm to room temperature slowly. This reagent solution (1.0 ml, 1.0 mmol) was added to a solution of 3-fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline (322 mg, 1.0 mmol) and triethylamine (0.14 ml, 1.2 mmol) in dry methylene chloride at 5 °C under nitrogen. After
- 35 35 min, additional amounts of triethylamine (0.7 ml, 0.6 mmol) and aminosulfamoyl chloride solution (0.5 ml, 0.5 mmol) were added, and the reaction mixture was stirred for

an additional 15 min. The reaction mixture was diluted with ethyl acetate and water, and the organic layer was separated, washed with 1M sodium bisulfate and brine, and dried over magnesium sulfate. The solvent was removed *in vacuo* and the solid residue was triturated with ether to give 1-(3-fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-phenyl)sulfamide (303 mg, 75%) as a tan powder.

- b) Proceeding as described in Example 23, but substituting 3-fluoro-4-[5-(2,4-dimethyl-benzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline [prepared by the method described in Example 6], for 3-fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline gave 1-(3-fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl)sulfamide.
- c) Proceeding as described in Example 23, but substituting 3-fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline [prepared by the method described in Example 1, but substituting the methyl ester of zomepirac for ethyl 5-benzoyl-1,4-dimethylpyrrole-2-acetate in Step (b)], for 3-fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline gave 1-(3-fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl)sulfamide.
- d) Proceeding as described in Example 23, but substituting 3-cyano-4-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline [prepared by the method described in Example 6, but substituting 4-methoxybenzoyl chloride for 2,4-dimethylbenzoyl chloride in Step (b) and 3-cyano-4-chloronitrobenzene for 3,4-difluoro-nitrobenzene in Step (c)], for 3-fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline gave 1-(3-cyano-4-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl)sulfamide.
- e) Proceeding as described in Example 23, but substituting {2-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}amine [prepared by the method described in Example 5, but substituting the methyl ester of tolmetin for methyl 5-(4-methylbenzoyl)-1-methylpyrrole-2-acetate in Step (b)], for 3-fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]aniline gave 1-{2-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-yl-methyl]pyridin-5-yl}sulfamide.

EXAMPLE 24Synthesis of 1-{4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]phenyl}-3-sulfamorpholide

5

1-{4-[5-(4-Chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3,3-dimethylsulfamide (75 mg, 0.188 mmol) and triethylamine (0.047 ml, 0.376 mmol) were dissolved in benzene (0.4 ml). The reaction mixture was stirred for 15 min and then concentrated *in vacuo*. The yellow solid residue was redissolved in 1.0 ml of morpholine and heated at 65 °C for 24 h. The reaction mixture was partitioned between ethyl acetate and 5% aqueous HCl. The organic layer was separated, washed with water, and brine, and dried over sodium sulfate. Crystallization of the crude product from hexane-ethyl acetate gave 1-{4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-3-sulfamorpholide (49 mg, 53%) as a solid, mp 126-127 °C.

15

EXAMPLE 25Synthesis of N-{2-hydroxy-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]phenyl}methanesulfonamide

20

N-{2-Benzoyloxy-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide (0.31 g, 0.59 mmol) was dissolved in ethyl acetate (50 ml). 10% Pd/C (93 mg) was added and the mixture was stirred under H<sub>2</sub> atmosphere for 2h. The mixture was filtered through Celite<sup>®</sup> and the filtrate was evaporated to give a solid. Crystallization from hexane-acetone gave N-{2-hydroxy-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]phenyl}-methanesulfonamide (200 mg, 78%) as a solid, mp 205 °C (dec.)

25

30

EXAMPLE 26Synthesis of N-{3-carboxy-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]phenyl}methanesulfonamide

35

N-{3-Methoxycarbonyl-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl-methyl]phenyl}methanesulfonamide (735 mg, 1.54 mmol) and 2.5 N sodium hydroxide



(2.5 ml) were dissolved in a 1:1 mixture of methanol-THF (40 ml) and stirred at room temperature for 64 h. The mixture was diluted with water, acidified to pH 2 with 2.0 N HCl, and extracted with ethyl acetate. The organic extracts were washed with brine, dried over sodium sulfate and concentrated to dryness. Crystallization from methylene chloride-methanol gave N-{3-carboxy-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]phenyl}-methanesulfonamide (500 mg, 70%) as a solid, mp 248-250 °C (dec.).

#### EXAMPLE 27

10      Synthesis of N-{3-cyano-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-phenyl}methanesulfonamide

N-{3-Bromo-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-methane-sulfonamide (320 mg, 0.69 mmol) was dissolved in DMF. CuCN (120 mg, 1.38 mmol) was added and the suspension was refluxed for 4 h. The mixture was cooled to room temperature, and NaCN (2.0 g in 10 ml of water) was added. After 0.5 h the mixture was extracted with ethyl acetate and the extracts were washed with water, and brine, and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by preparatory TLC (hexane-ethyl acetate) to give N-{3-cyano-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-yl-methyl]phenyl}methanesulfonamide (190 mg, 67%) as a solid, mp 171-172 °C.

#### EXAMPLE 28

25      Synthesis of 3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline

3-Fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline (5.0 g, 14.0 mmol), sodium acetate (1.15 g, 14 mmol) and 10% Pd/C (475 mg) were suspended in ethanol (230 ml). The reaction mixture was shaken in a Parr apparatus under hydrogen atmosphere at 30 psi overnight. The mixture was filtered through Celite® and the filtrate was evaporated to dryness. The crude product was purified on a silica gel column (methylene chloride-methanol, 99:1) and then crystallized from ethyl acetate/hexane/cyclohexane to give 3-fluoro-4-[5-benzoyl-1,4-dimethyl-1H-pyrrol-2-yl-methyl]aniline (2.49 g, 55%) as a solid.

EXAMPLE 29Synthesis of 3-fluoro-4-[5-(4-methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline

5                   3-Fluoro-4-[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline (2.0 g, 5.6 mmol) was dissolved in degassed DMF. Sodium thiomethoxide (1.5g, 22.4 mmol) was added and the mixture stirred at room temperature under argon for 24 h. The reaction  
10 was poured into ice-water, acidified with acetic acid to pH 3 and extracted with ethyl acetate. The organic extracts were washed with water, and brine, and dried over magnesium sulfate. The solvent was removed *in vacuo* and the crude product was purified on a silica gel column (methylene chloride-methanol-acetone, 96:2:2) to give 3-fluoro-4-[5-(4-methylthiobenzoyl)-1,4-dimethyl-1H-pyrrol-2-ylmethyl]aniline (1.13 g, 55%) as a  
15 solid, mp 199.1-199.7 °C.

EXAMPLE 30

20                   The following are representative pharmaceutical formulations containing a compound of formula I.

Tablet formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

25	Ingredient	Quantity per tablet, mg
	compound of this invention	400
	cornstarch	50
	croscarmellose sodium	25
30	lactose	120
	magnesium stearate	5

Capsule formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

5		
	Ingredient	Quantity per capsule, mg
	compound of this invention	200
	lactose, spray-dried	148
10	magnesium stearate	2

Suspension formulation

The following ingredients are mixed to form a suspension for oral administration.

15		
	Ingredient	Amount
	compound of this invention	1.0 g
	fumaric acid	0.5 g
	sodium chloride	2.0 g
20	methyl paraben	0.15 g
	propyl paraben	0.05 g
	granulated sugar	25.5 g
	sorbitol (70% solution)	12.85 g
	Veegum K (Vanderbilt Co.)	1.0 g
25	flavoring	0.035 ml
	colorings	0.5 mg
	distilled water	q.s. to 100 ml

Injectable formulation

The following ingredients are mixed to form an injectable formulation.

5	<b>Ingredient</b>	<b>Amount</b>
	compound of this invention	0.2 g
	sodium acetate buffer solution, 0.4 M	2.0 ml
	HCl (1N) or NaOH (1N)	q.s. to suitable pH
	water (distilled, sterile)	q.s. to 20 ml

10

Topical formulation

A topical formulation is prepared with the following ingredients.

15	<b>Ingredient</b>	<b>Amount, g</b>
	compound of this invention	10
	Span 60	2
	TWEEN®60	2
	mineral oil	5
20	petrolatum	10
	methyl paraben	0.15
	propyl paraben	0.05
	BHA (butylated hydroxy anisole)	0.01
	water	q.s. to 100

25

All of the above ingredients, except water, are combined and heated to 60-70°C with stirring. A sufficient quantity of water at 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository formulation

A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

compound of the invention	500 mg
Witepsol® H-15	balance

10

EXAMPLE 31Inhibition of COX I and COX II *in vitro*

The COX I and COX II inhibitory activity of compounds of this invention *in vitro* was determined using partially purified COX I and COX II enzymes, prepared as described in J. Barnett et al., *Biochim. Biophys. Acta*, **1209**:130-139 (1994).

COX I and COX II samples were diluted with Tris-HCl buffer (50mM Tris-HCl, pH 7.9) containing 2 mM EDTA and 10% glycerol and reconstituted by incubating first with 2 mM phenol for 5 minutes and then with 1 micromolar hematin for an additional 5 minutes. 125 ml of the reconstituted COX I or COX II enzyme were preincubated for 10 minutes at room temperature in a shaking water bath with the compounds of the invention dissolved in 2-15 ml of DMSO or the carrier vehicles (control samples). The enzyme reaction was initiated by adding 25 ml of 1-[<sup>14</sup>C]arachidonic acid (80,000-100,000 cpm/tube; 20 micromolar final concentration) and the reaction was allowed to continue for an additional 45 seconds. The reaction was terminated by adding 100 ml of 2 N HCl and 750 ml water. An aliquot (950 ml) of the reaction mixture was loaded onto a 1 ml C<sub>18</sub> Sep-Pak column (J.T. Baker, Phillipsburg, NJ) which had been previously washed with 2-3 ml methanol and equilibrated with 5-6 ml distilled water. Oxygenated products were quantitatively eluted with 3 ml of acetonitrile/water/acetic acid (50:50:0.1, v/v) and the radioactivity in the eluate determined in a scintillation counter.

Compounds of this invention were active in this assay.

The COX inhibitory activities (expressed as  $IC_{50}$ , the concentration causing 50% inhibition of the COX enzyme being assayed) of some compounds of the invention and indomethacin as a comparator, were:

CPD#	COX I $IC_{50}$ , m M	COX II $IC_{50}$ , m M	CPD#	COX I $IC_{50}$ , m M	COX II $IC_{50}$ , m M
1	11	0.15	206	0.46	0.24
11	7.5	0.51	222	0.46	0.074
19	0.76	0.08	223	0.064	0.029
27	415	0.063	226	100	2.1
28	33	0.19	227	2.5	0.1
31	3.9	0.045	228	8.5	0.1
36	10	0.05	235	8.2	0.17
38	0.27	0.065	236	15	0.51
48	61	0.08	243	100	8.9
60	0.16	0.028	250	34	27.4
63	0.035	0.33	251	310	0.64
66	6.9	0.12	263	49	0.45
68	0.86	0.073	267	210	0.7
71	38	0.16	271	89	0.43
72	265	0.7	272	>1000	2.1
88	<0.1	0.06	276	60	0.5
95	0.09	0.06	284	22	0.50
97	<0.1	0.038	288	235	0.55
98	< 0.1	0.23	289	10.2	1.5
104	0.75	0.24	294	9.1	2.6
106	0.95	0.07	295	0.60	0.10
131	0.20	0.077	296	0.21	0.40
133	0.045	0.058	306	113	0.64
140	5.4	0.12	308	650	8.75
141	3.9	0.03	310	142	9.2
146	2.9	0.06	314	65	0.56
147	0.6	0.1	316	360	0.20
154	34	0.054	329	256	43.7

165	16.8	0.095	330	61.1	30
172	43	0.09	333	NA	78.4
177	0.79	0.30	334	18.3	0.64
196	5.0	0.04	340	0.02	0.06
197	<0.1	0.07	343	6.6	0.54
202	3.2	0.05	Indo-methacin	0.4	14

### EXAMPLE 32

#### Anti-inflammatory activity

5

The anti-inflammatory activity of compounds of this invention was determined by measuring the inhibition of carrageenan-induced paw edema in the rat, using a modification of the method described in Winter C. A. et al. (1962) "Carrageenan-Induced Edema in Hind Paw of the Rat as an Assay for Anti-inflammatory Drugs". *Proc. Soc. Exp. Biol. Med.* **111**: 544-547. This assay has been used as a primary *in vivo* screen for anti-inflammatory activity of most NSAIDs, and is considered predictive of human efficacy. Briefly, test materials were administered orally to female rats in a volume of 1ml prepared as solutions or suspensions in an aqueous vehicle containing 0.9% NaCl, 0.5% sodium carboxymethyl-cellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol and 97.3% distilled water. Control rats received vehicle alone. After 1 h 0.05 ml of a 0.5% solution of Carrageenan (Type IV Lambda, Sigma Chemical Co.) in 0.9% saline was injected into the subplantar region of the right hind paw. Three hours later the rats were euthanized in a carbon dioxide atmosphere; hind paws were removed by severing at the tarso-crural joint; and the left and right paws were weighed. The increase in weight of the right paw over the left paw was obtained for each animal and the mean increases were calculated for each group. The anti-inflammatory activity of the test materials is expressed as the percent inhibition of the increase in hind paw weight of the test group relative to the vehicle-dosed control group.

Compounds of this invention were active in this assay.

25 The anti-inflammatory activities (expressed as % inhibition) of some of the compounds of the invention at 10mg/Kg were:

CPD#	% Inhibition	CPD#	% Inhibition
19	36	146	40
36	31	165	17
48	35	263	40
98	42	288	20
140	27	343	35

### EXAMPLE 33

5

#### Inhibition of eicosanoid synthesis *in vivo*

The activity of compounds of this invention in inhibiting *in vivo* eicosanoid (prostaglandin E<sub>2</sub>) synthesis in inflamed tissues was determined by the carrageenan-induced inflammation (air-pouch model) in rats, using a modification of the method described in

10 Futaki, M., et al.; (1993) "Selective Inhibition of NS-398 on prostanoid production in inflamed tissue in rat Carrageenan Air-pouch Inflammation" *J. Pharm. Pharmacol.* **45**:753-755, and Masferrer, J.L., et al.; (1994) "Selective Inhibition of inducible cyclooxygenase 2 *in vivo* is Antiinflammatory and Nonulcerogenic" *Proc. Natl. Acad. Sci. USA.* **91**: 3228-3232. In this assay, an air-pouch is created in the rat and the PGE<sub>2</sub> levels in the air-pouch

15 exudate are measured by enzyme immunoassay. Briefly, male rats were anesthetized using a 60:40 CO<sub>2</sub>:O<sub>2</sub> mixture and subsequently injected subcutaneously with 20 ml of sterilized air, under aseptic conditions, in the proximal area of the dorsum. This injection of sterile air causes the creation of a subcutaneous "air pouch". The next day, a further 10 ml of sterile air was injected into the previously formed pouch using the same technique. The test

20 materials were administered orally in a volume of 1ml/100g body weight as solutions or suspensions in an aqueous vehicle containing 0.9% NaCl, 0.5% sodium carboxymethyl-cellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol and 97.3% water. Control rats received vehicle alone. After 30 minutes, 5ml of a 0.5% solution of carrageenan (Sigma, Lambda Type IV) was injected into the air pouch. The rats were euthanized 3 or 6 h after

25 the compound administration. 10 ml of a solution containing 10 mg/l of indomethacin and 5.4 mM EDTA in 0.9% sterile saline was injected into the air pouch; the air pouch was cut open; and the exudate was harvested. The total exudate volume was recorded, and the



samples were analyzed for PGE<sub>2</sub> and 6-keto PGF<sub>1</sub> by ELISA (Titerzyme<sup>®</sup>, PerSeptive Diagnostics) and TxB<sub>2</sub> by radioimmuno assay (New England Nuclear Research, Catalog No. NEK-037), according to the manufacturer's directions.

- 5 The mean concentrations of PGE<sub>2</sub> were calculated for each group. The anti-inflammatory activity of test materials is expressed as the percent inhibition of PGE<sub>2</sub> formation in the test group relative to the control group.

Compounds of this invention were active in this assay.

10

The anti-inflammatory activities (expressed as % inhibition of air pouch PGE<sub>2</sub> formation) of some of the compounds of this invention and indomethacin as a comparator were:

CPD#	Dose mg/Kg	% Inhibition	Time
19	10	74%	3 hr
36	10	96%	3 hr
48	30	64%	3 hr
98	10	98%	3 hr
140	30	83%	6 hr
146	10	93%	3 hr
165	10	52%	3 hr
236	30	71%	6 hr
263	30	80%	6 hr
271	10	56%	3 hr
284	10	65%	3 hr
288	10	53%	3 hr
334	10	44%	3 hr
Indomethacin	2-5	>70%	

EXAMPLE 34Analgesic Activity

5 The analgesic activity of compounds of this invention may be determined by the Acetic Acid-induced Rat Writhing Assay, using a modification of the method described in Berkenkopf, J.W. and Weichman, B.M. "Production of Prostacyclin in Mice following Intraperitoneal Injection of Acetic Acid, Phenylbenzoquinone and Zymosan: Its Role in the Writhing Response" *Prostaglandins*: 36: 693-70 (1988). This assay is one of several acute  
10 assays which have been used to assess the analgesic activity of NSAIDs, and is considered predictive of human efficacy. The test materials were administered orally to male Sprague Dawley rats in a volume of 1ml/100g body weight as solutions or suspensions in an aqueous vehicle containing 0.9% NaCl, 0.5% sodium carboxymethyl-cellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol and 97.3% water. Control rats received vehicle alone.  
15 One hour after compound administration, 0.3 ml/100g body weight of 0.75% solution of acetic acid was injected intraperitoneally. The acetic acid injection induces a series of characteristic writhing responses, which were counted over the period between 15 and 30 minutes after the injection. The analgesic activity of test materials is expressed as the percentage inhibition of writhing in the test group relative to the control group.

20

Compounds of this invention were active in this assay.

The analgesic activities (expressed as % inhibition of writhing responses) of some of the compounds of this invention at 10mg/Kg were:

25

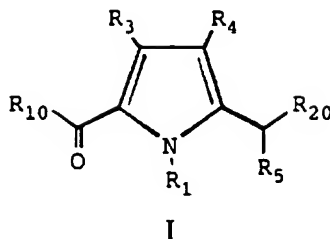
CPD#	% Inhibition	CPD#	% Inhibition
36	16	140	4
98	71	263	31

The analgesic activity of compounds of this invention may also be determined using an adjuvant-induced arthritis pain model in the rat, where pain is assessed by the animal's vocal response to the squeezing or flexing of an inflamed ankle joint, as described in Winter  
30 C.A. and Nuss, G.W. (1966) "Treatment of Adjuvant Arthritis in rats with Antiinflammatory Drugs" *Arthritis Rheum.* 9: 394-403 and Winter, C.A., Kling P.J.,

Tocco, D.J., and Tanabe, K. (1979). "Analgesic activity of Diflunisal [MK-647; 5-(2,4-Difluorophenyl)salicylic acid] in Rats with Hyperalgesia Induced by Freund's Adjuvant" *J. Pharmacol. Exp. Ther.* **211**: 678-685.

Claims

1. A compound of the formula I:

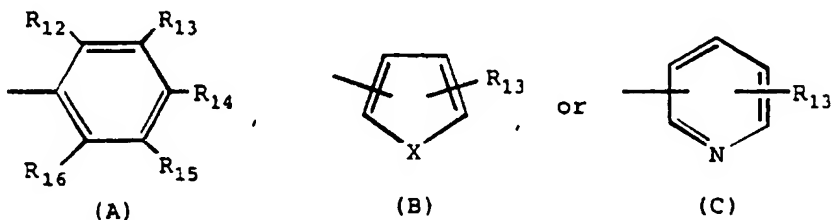


where:

$R_1$  and  $R_5$  are independently H or alkyl, or  $R_1$  and  $R_5$  together are  $-(CH_2)_2-$  or  $-(CH_2)_3-$ ;

$R_3$  and  $R_4$  are independently H, halo, alkyl, alkyloxy, or alkylthio;

$R_{10}$  is a group represented by formula (A), (B) or (C):



where:

X is O or S;

$R_{12}$  and  $R_{16}$  are independently H, halo, alkyl, alkyloxy, alkylthio, cyano, or hydroxy;

$R_{13}$  and  $R_{15}$  are independently H, halo, alkyl, alkyloxy, or alkylthio; and

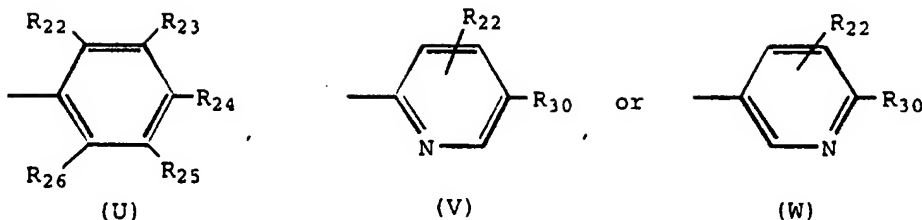
$R_{14}$  is H, halo, alkyl, haloalkyl, amino, alkylamino, dialkylamino, alkyloxy, hydroxy, alkylthio, alkenyl, alkynyl, cyano,  $-SO_2R_{17}$  where  $R_{17}$  is alkyl, or  $-SO_2NR_{18}R_{19}$  where  $R_{18}$  and  $R_{19}$  are independently H or alkyl;

provided that at least two of  $R_{12}$ ,  $R_{13}$ ,  $R_{14}$ ,  $R_{15}$  and  $R_{16}$  are H, and that if only two of  $R_{12}$ ,

$R_{13}$ ,  $R_{14}$ ,  $R_{15}$ , and  $R_{16}$  are H, the non-hydrogen substituents are not all adjacent; or

$R_{12}$ ,  $R_{15}$ , and  $R_{16}$  are H and  $R_{13}$  and  $R_{14}$  together are  $-OCH_2O-$ ;

$R_{20}$  is a group represented by formula (U), (V) or (W):



where:

R<sub>22</sub> is H, halo, alkyl, cyano, trifluoromethyl, hydroxy, alkyloxy, or -CO<sub>2</sub>R<sub>27</sub> where R<sub>27</sub> is H or alkyl;

- 5 one of R<sub>23</sub>, R<sub>24</sub>, and R<sub>25</sub> is R<sub>30</sub>; and  
 either all the remaining R<sub>23</sub>, R<sub>24</sub>, R<sub>25</sub>, and R<sub>26</sub> are H; or one of the remaining R<sub>23</sub>, R<sub>24</sub>, R<sub>25</sub>, and R<sub>26</sub> is halo, alkyl, cyano, trifluoromethyl, hydroxy, or alkyloxy; and  
 R<sub>30</sub> is -OH\*, -NHH\*, -NH\*CHO, -NH\*C(X)R<sub>31</sub>, -NH\*SO<sub>2</sub>R<sub>31</sub>,  
 -NH\*C(X)NR<sub>32</sub>R<sub>33</sub>, or -NH\*SO<sub>2</sub>NR<sub>32</sub>R<sub>34</sub>,

10 where:

H\* is hydrogen, optionally replaced by an *in vivo* hydrolyzable protecting group;

R<sub>31</sub> is alkyl, haloalkyl, hydroxyalkyl, alkenyl, benzyl, aryl, cycloamino, -CH<sub>2</sub>SO<sub>2</sub>Me, or -(CH<sub>2</sub>)<sub>n</sub>R<sub>35</sub>, where n is an integer from 2 to 5 and R<sub>35</sub> is alkylamino, dialkylamino, cycloamino, alkyloxy, acyloxy, or -CO<sub>2</sub>R<sub>27</sub>;

- 15 R<sub>32</sub> is H, alkyl, or -(CH<sub>2</sub>)<sub>n</sub>OR<sub>27</sub>;

R<sub>33</sub> is H, alkyl, haloalkyl, aryl, hydroxyalkyl, tetrahydrofuran-2-ylmethyl, -CH<sub>2</sub>CO<sub>2</sub>R<sub>27</sub>, or -(CH<sub>2</sub>)<sub>n</sub>R<sub>35</sub>; and

R<sub>34</sub> is H, alkyl, acetyl, hydroxyalkyl, or -(CH<sub>2</sub>)<sub>n</sub>R<sub>35</sub>;  
 and their pharmaceutically acceptable salts.

20

2. A compound of Claim 1 where R<sub>20</sub> is a group represented by formula (U) or (V) and R<sub>24</sub> is R<sub>30</sub>.

3. A compound of Claim 2 where R<sub>10</sub> is a group represented by formula (A) and R<sub>1</sub> is  
 25 alkyl.

4. A compound of Claim 3 where R<sub>3</sub> is H or alkyl; R<sub>4</sub>, R<sub>5</sub>, R<sub>15</sub>, and R<sub>16</sub> are H; and R<sub>13</sub> is H, halo, or alkyl.

30 5. A compound of Claim 4 where R<sub>30</sub> is -NHH\*, -NH\*SO<sub>2</sub>R<sub>31</sub>, or -NH\*SO<sub>2</sub>NR<sub>32</sub>R<sub>34</sub>.

6. A compound of Claim 5 where  $R_1$  is Me;  $R_3$  is H or Me;  $R_{13}$  is H; and  $R_{14}$  is H, halo, alkyl, alkylthio, or alkoxy.
7. A compound of Claim 6 where  $R_{12}$  is H, F, Cl, Me, OMe, or OH; and  $R_{14}$  is H, F, Cl, Me, OMe, or SMe.
8. A compound of Claim 7 where  $R_{20}$  is a group represented by formula (U);  $R_{23}$  and  $R_{25}$  are H; and  $R_{22}$  and  $R_{26}$  are independently H, halo, or cyano.
9. A compound of Claim 8 where  $R_{14}$  is H, Me, Cl or OMe; and  $R_{22}$  and  $R_{26}$  are independently H, F, Cl, or CN.
10. A compound of Claim 9 where  $R_{26}$  is H.
11. A compound of Claim 10 where  $R_{30}$  is  $-NH^*SO_2R_{31}$ .
12. A compound of Claim 11 where  $R_{31}$  is alkyl, hydroxyalkyl, or  $-(CH_2)_nR_{35}$ .
13. A compound of Claim 12 where  $R_{31}$  is Me or 2-hydroxyethyl.
14. The compound of Claim 13 where  $R_3$  is H;  $R_{12}$  and  $R_{14}$  are Me;  $R_{22}$  is F; and  $R_{31}$  is 2-hydroxyethyl, namely N-{3-fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
15. The compound of Claim 13 where  $R_3$  is H;  $R_{12}$  and  $R_{14}$  are H;  $R_{22}$  is F; and  $R_{31}$  is 2-hydroxyethyl, namely N-{3-fluoro-4-[5-benzoyl-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
16. The compound of Claim 13 where  $R_3$  is H;  $R_{12}$  is H;  $R_{14}$  is Me;  $R_{22}$  is F; and  $R_{31}$  is 2-hydroxyethyl, namely N-{3-fluoro-4-[5-(4-methylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]phenyl}-2-(hydroxy)ethanesulfonamide.
17. A compound of Claim 10 where  $R_{30}$  is  $-NH^*SO_2NR_{32}R_{34}$ .
18. A compound of Claim 17 where  $R_{32}$  is H; and  $R_{34}$  is H or acetyl.

19. The compound of Claim 18 where  $R_3$  is H;  $R_{12}$  and  $R_{14}$  are Me;  $R_{22}$  is F; and  $R_{34}$  is H, namely 1-(3-fluoro-4-[5-(2,4-dimethylbenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]-phenyl)sulfamide.
- 5 20. A compound of Claim 10 where  $R_{30}$  is -NHH\*.
21. A compound of Claim 20 where  $R_3$  is H;  $R_{12}$  and  $R_{14}$  are Me; and  $R_{22}$  is F.
22. A compound of Claim 7 where  $R_{20}$  is a group represented by formula (V);  $R_{14}$  is  
10 Me, Cl, or OMe; and  $R_{22}$  is H, F, or Cl.
23. A compound of Claim 22 where  $R_{30}$  is -NH\*SO<sub>2</sub> $R_{31}$ .
24. A compound of Claim 23 where  $R_{31}$  is alkyl, hydroxyalkyl, or -(CH<sub>2</sub>)<sub>n</sub> $R_{35}$ .  
15
25. A compound of Claim 24 where  $R_{31}$  is Me.
26. The compound of Claim 25 where  $R_3$ ,  $R_{12}$ , and  $R_{22}$  are H; and  $R_{14}$  is OMe, namely  
N-{2-[5-(4-methoxybenzoyl)-1-methyl-1H-pyrrol-2-ylmethyl]pyridin-5-yl}-  
20 methanesulfonamide.
27. A compound of Claim 22 where  $R_{30}$  is -NH\*SO<sub>2</sub>NR<sub>32</sub> $R_{34}$ .
28. A compound of Claim 27, where  $R_{32}$  is H; and  $R_{34}$  is H or acetyl.  
25
29. A compound of Claim 22 where  $R_{30}$  is -NHH\*.
30. A compound of Claim 29 where  $R_3$ ,  $R_{12}$ , and  $R_{22}$  are H; and  $R_{14}$  is OMe.
- 30 31. The compounds of any one of claims 1-30 as medicaments.
32. A pharmaceutical composition particularly for the treatment of an inflammatory  
disease or an autoimmune disease comprising a therapeutically effective amount of a  
compound of Claim 1 and a pharmaceutically acceptable excipient.  
35

33. The use of a compound of any one of claims 1-30 in the manufacture of a pharmaceutical composition for the treatment of an inflammatory disease or an autoimmune disease.
- 5 34. The novel compounds, compositions substantially as described hereinbefore, particularly with reference to the Examples.

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/02587

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D207/32 C07D207/34 C07D487/04 C07D405/12 C07D401/06  
C07D409/14 C07D405/14 C07D409/06 A61K31/40 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 752 826 A (J.R. CARSON) 14 August 1973 see column 1, line 24 - column 2, line 30 ---	1,31-33
A	US 4 089 969 A (J.M. MUCHOWSKI ET AL) 16 May 1978 see column 1, line 8 - column 2, line 44 ---	1,31-33
A	H.-P. KAISER ET AL: J. ORG. CHEM., vol. 49, no. 22, 1984, pages 4203-4209, XP002041191 see page 4205, scheme III, formula 15 ---	1
A	EP 0 292 979 A (FUJISAWA PHARMACEUTICAL CO LTD) 30 November 1988 see page 3, lines 1-41 and page 10, lines 3-4 ---	1,31-33
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \* "A" document defining the general state of the art which is not considered to be of particular relevance
- \* "E" earlier document but published on or after the international filing date
- \* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \* "O" document referring to an oral disclosure, use, exhibition or other means
- \* "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\* "&" document member of the same patent family

Date of the actual completion of the international search

19 September 1997

Date of mailing of the international search report

6. 10. 97

Name and mailing address of the ISA

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Authorized officer

Van Amsterdam, L

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 97/02587

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	EP 0 714 895 A (F. HOFFMANN-LA ROCHE AG) 5 June 1996 see claims 10,11,14,20 -----	1,31-33

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 97/02587

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 34  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
It is not clear which compounds fall within the scope of claim 34.
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/02587

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3752826 A	14-08-73	US 3865840 A	11-02-75
		AT 313268 A,B	15-01-74
		AT 308735 A,B	15-06-73
		AT 313270 A,B	15-01-74
		AT 313271 A,B	15-01-74
		BE 762060 A	26-07-71
		CA 924728 A	17-04-73
		CH 566984 A	30-09-75
		CH 547279 A	29-03-74
		DE 2102746 A	12-08-71
		FR 2081455 A	03-12-71
		GB 1327308 A	22-08-73
		IN 140718 A	11-12-76
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		JP 55033401 A	08-03-80
		JP 58002935 B	19-01-83
		JP 1169895 C	17-10-83
		JP 55033402 A	08-03-80
		JP 58002936 B	19-01-83
		JP 1152312 C	30-06-83
		JP 55162767 A	18-12-80
		JP 57045428 B	28-09-82
		JP 1235983 C	17-10-84
		JP 55162766 A	18-12-80
		JP 59001711 B	13-01-84
		NL 7101016 A	28-07-71
		SE 389670 B	15-11-76
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